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Molecular Docking of Inhibitory Activities of *Syzygium Cordatum* against Mycobacterium Tuberculosis

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ABSTRACT

Tuberculosis remains a significant infectious disease-causing over 1.8 million deaths a year, making it one of the world's most deadly human pathogens. Phytochemicals from natural products are intensely becoming alternative sources of antimicrobial agents with striking mechanisms of action and common side effects compared to synthetic drugs such as isoniazid (−4.7 kcal/mol), pyrazinamide (−4.4 kcal/mol), and ethambutol (−4.5 kcal/mol). Isolated phytochemicals from the bark of Syzygium cordatum were evaluated for antimicrobial activity against mycobacterium tuberculosis through molecular docking. It was observed that quite a number of the phytochemicals have good binding affinities much better than those of the commonly used first-line drugs. Pharmacokinetics analysis of these phytochemicals revealed that binding affinity alone is not enough to prove the potency of a promising drug candidate. Only 7 compounds among the 18 screened compounds passed all the analyses and are identified as potential mycobacterium tuberculosis (4RHT) inhibitors. This study thereby recommends 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) as potential inhibitors of mycobacterium tuberculosis (4 RHT) with better pharmacokinetics and bioavailability.

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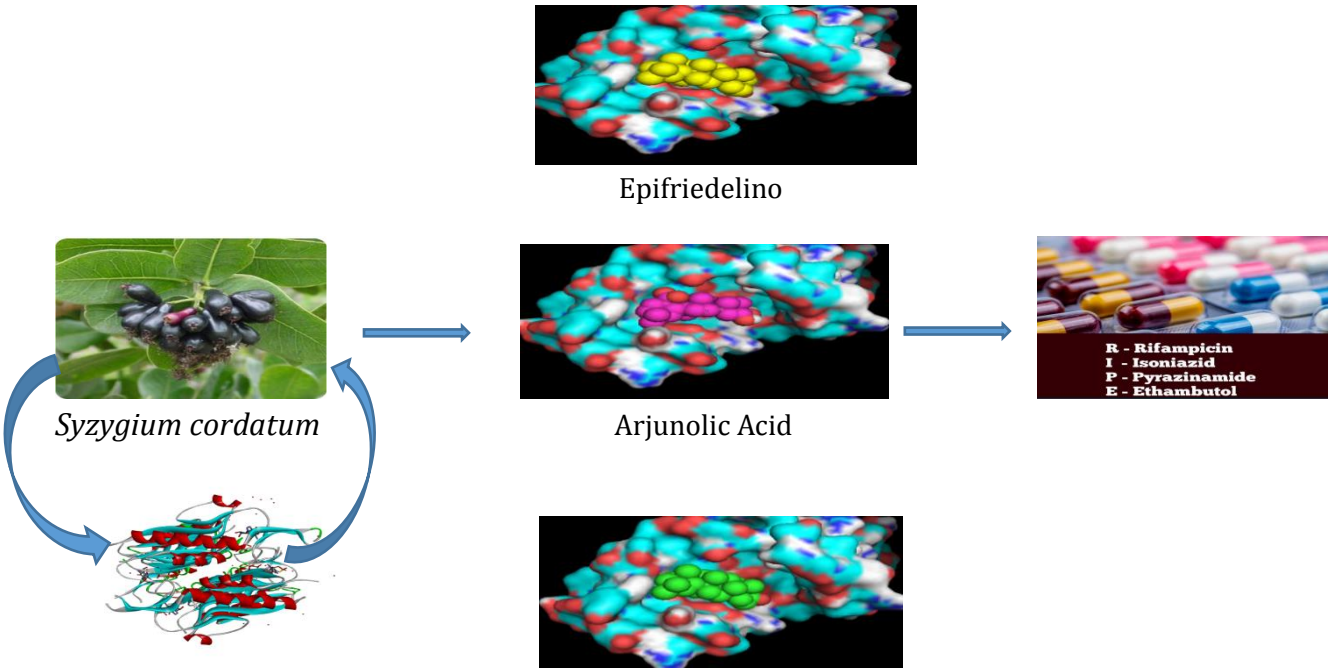
GRAPHICAL ABSTRACT



Introduction

Tuberculosis (TB) remains one of the significant infectious diseases causing over 1.8 million deaths a year, making it one of the world's most deadly human pathogen [1]. World Health Organization (WHO) reported that 10 million people were estimated to fall ill with TB in 2019 globally. Men ≥18 years were primarily accounted for 56%, while women and children ≤15 accounted for 44%. Despite 9% and 14% cumulative reduction between 2015 to 2019 in the incidence rate and death rate of TB, respectively [2], tuberculosis (TB) remains a significant public health problem, especially in the developing and low-income countries where access to quality and innovative diagnoses and TB treatment coupled with good nourishment to sustain the long regimen treatment could be a challenging task. This necessitates studying and developing new prevention protocols and treatments for TB. Hence, governments of all nations, public health policymakers, supranational organizations, and governing bodies need to make funds available, accessible, and optimally used for TB research, prevention, diagnosis, and treatment. WHO has recommended these four first-line drugs: Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide for treating active, drug-susceptible TB in a 6-month regimen treatment. However, research has shown that TB has proven to be multi-drug resistant and extensively drug-resistant to at least two first-line drugs: Isoniazid and Rifampicin [3]. Among the notable factors responsible for this are poor regimen selection, inadequate drug supply, and patients' poor adherence to the drug regimen over a long period. Hence, there is a need for short-termed, less costly, and effective drugs in combating this die-hard disease. The rapid development of drug-resistant microbes has pushed the search for novel chemical compounds to discover drugs in treating life-threatening human diseases [4]. Natural Products are a safe option due to low

production costs, structural diversity, and multiple uses of active compounds in treating diverse diseases. Natural products can target microbial pathogens, which is of interest in the scientific and medical communities since infectious diseases are the leading cause of human mortalities globally.

Syzygium cordatum (Myrtaceae) well known in English as water berry; in Congo as cikobarhi; in Kenya as karumaa, kivueni, kumusemwa; in Malawi as nanyowe, nyowe; in Southern Africa as umdoni, waterbessie;in Zulu as umJomi, umSwi; in Xhosa as umCozi; in Swazi as muhlwa, muthwa, onDoni; in Tsonga or Thonga as montlho, motlho; in Tanzania: awartu, ijiraombe. Its related wild species (*Syzygium guineese*) found in Nigeria is known as Adere or Ori-ira inYoruba, Malmoo in Hausa [5]. It is a valuable medicinal plant usually found near the riverbank, on the swamp forest border, on the savanna edge in many parts of Africa. It grows to 8 to 15 m and is known for its many uses. *Syzygium cordatum* was reported for itsmultipurpose use in Swaziland as herbal medicine, edible fruits, and other domestic livelihoods. Traditional medicinal practitioners used the concoction, decoction, infusion, or extracts prepared from diverse parts of S. cordatum as medicines in treating significant ailments such as common colds, cough, tuberculosis (TB), and other respiratory complaints, diarrhea, dysentery, stomach aches, burns, sores, wounds, sexually transmitted infections (STIs), fever, malaria, diabetes mellitus and glucose intolerance [6–8] in many parts of Africa. The ethnopharmacological review of S. cordatum identified almost a score of phytochemicals present in its bark [9].

Molecular docking is a computational method that virtually tries to predict with a substantial degree of accuracy the conformation of small-molecule (ligands) within appropriate target binding site (receptor), getting the best geometry of the ligand-receptor complex, and computing the interaction energy for various potential ligands to design novel drug candidate compounds. This study aims to screen eighteen(18) selected isolated compounds of the bark of *Syzygium cordatum* through molecular docking strategy with M. tuberculosis 6-oxopurine phosphoribosyltransferase(4RHT) as the receptor and identify a possible lead molecule as a template to design new hypothetical molecules with improved binding affinities, and better molecular residual interaction. In addition, in-silico absorption, distribution, metabolism, and excretion (ADME) and drug-likeness properties of the molecules were also analyzed.

Methodology

Ligand preparation

The bark of *Syzygium cordatum* plant was reported to contain almost eighteen (18) phytochemicals exhibiting anti-tubercular activity. Also, four first-line commonly used drugs in the treatment of *Mycobacterium tuberculosis* (MTB) were obtained [9,3]. PubChem [10] is the sole database where the phytochemicals and drug compounds were retrieved from SDF files and converted to protein data bank(PDB) format with the use of Biovia Discovery Studio software version 20.1.0.0 [11]. The ligands are Arjunolic acid, Caffeic acid, Cinnamic acid, Cyanidin, Delphinidin, Ellagic acid, Epifriedelinol, Epigallocatechin, Friedelin, Gallic acid, Glucose, Hesperidin, Hexahydroxydiphenic acid, Leucocyanidin, Leucodelphinidin, P-coumaric, Sinapic acid, and Tannin (Figure 1). At the same time, the first-line drugs are Ethambutol, Isoniazid, Pyrazinamide, and Rifampicin (Figure 2). ChemDraw professional software [12] was used to draw two-dimensional chemical structures of ligands and the drug compounds. The structures are saved in MDL.Mol(V2000) file format.

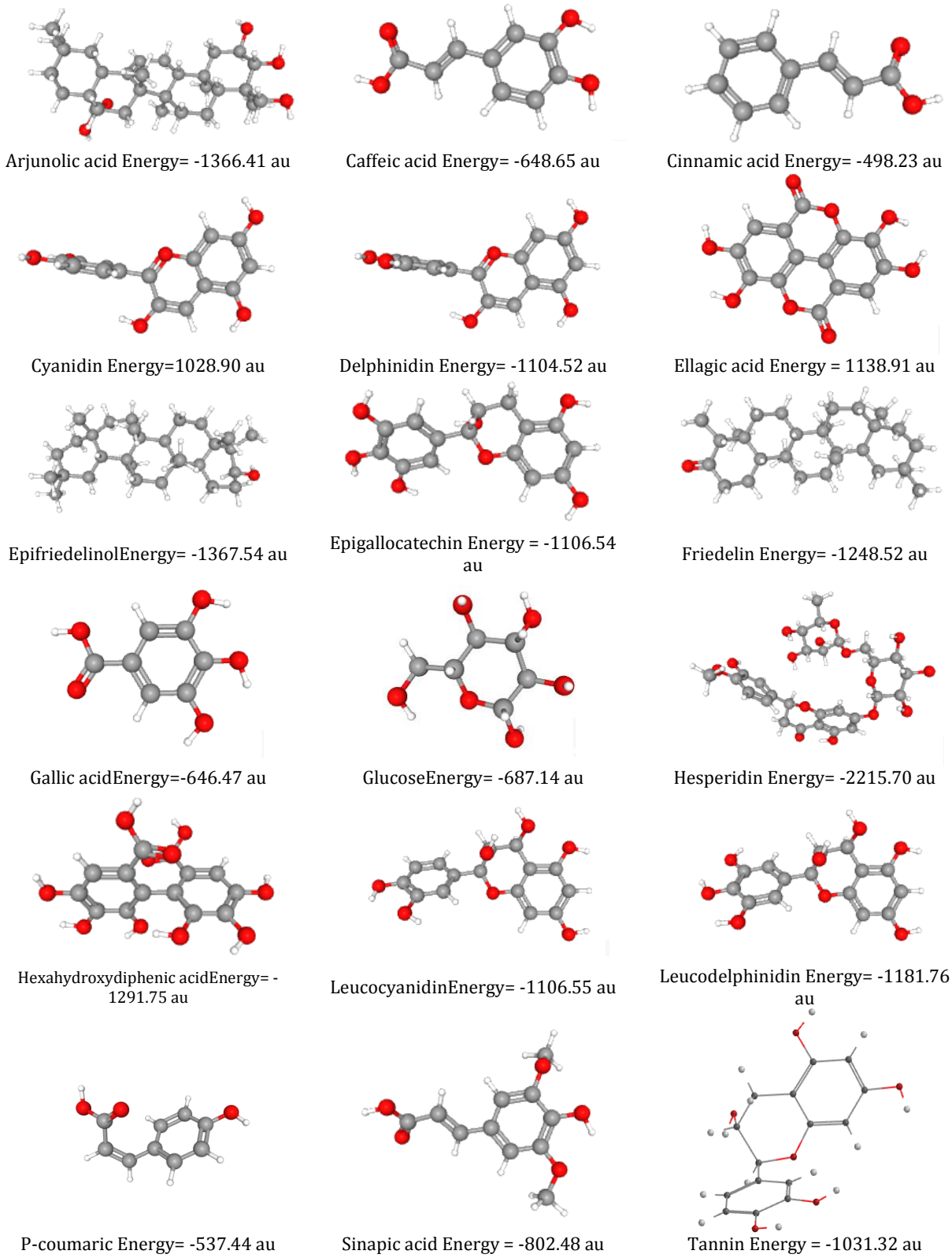
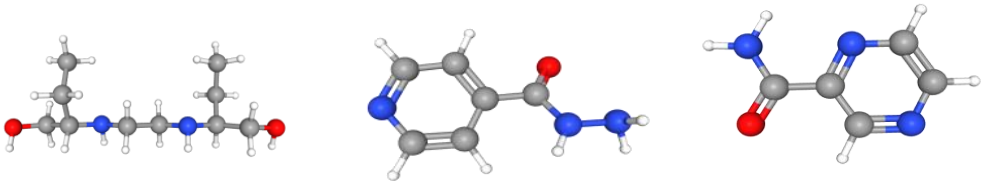
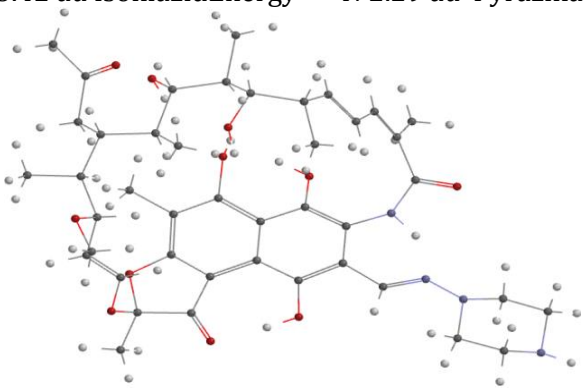


Figure 1. Structures of selected phytochemicals in the bark of *Syzyguim cordatum*



Ethambutol Energy = -655.42 au IsoniazidEnergy = -472.29 au Pyrazinamide Energy = -433.01 au



Rifampicin Energy = -2719.85 au

Figure 2. Structures of tuberculosis First-line drugs

Receptor preparation

The crystal structure of MTB-H37Rv (PDB ID: 4RHT) (Figure 3) was retrieved from the RCSB Protein Data Bank [13] in PDB format with an atomic resolution of 2.76 Å; a highly acceptable standard in pharmaceutical companies in designing therapeutic compounds. Heteroatoms and water molecules were removed from the crystal structures to avoid unwanted side molecular interactions and ensure no molecular interference with the potential binding site of the target protein during the docking simulation using Biovia [11] then saved in PDB format for further analysis. Alpha Beta–chain (D chain) was used for the docking study. This is because the protein exists as a tetramer with identical residues.

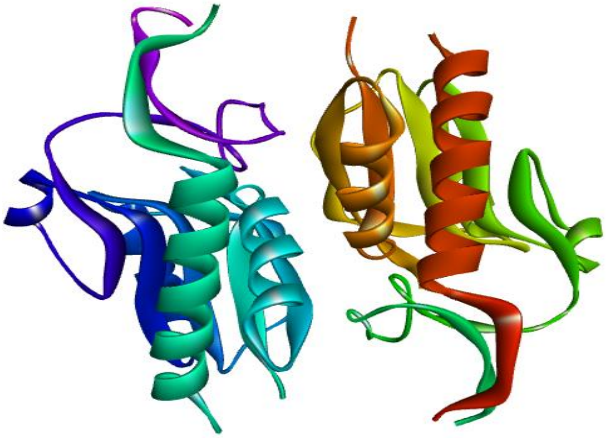


Figure 3. Crystal structure of tuberculosis protein (4RHT)

Determination of active sites of the receptor (4RHT)

Computed Atlas for Surface Topography of Proteins (CASTp) [14] and Biovia Discovery Studio [11] were used in validating the binding pocket, ligand interactions, and all amino acids in the active site of MTB complexed with 5GP, MG, POP ligands following the obtained experimental data[15].

Molecular docking simulation

AutoDock Vina, Vina Wizard, and open Babel of PyRx virtual screening software [16] were used for the docking studies. The docking output expressed in binding affinity/energy (kcal/mol) [17] shows the interaction energy between the protein and the Ligands/drug compounds, and the inhibition constant (K_i) in micromolar (μM) was depicted in Table 1. The energy of ligands was minimized to have a more stable configuration. The pose/conformation with the lowest B.E and the appropriate cluster was considered for further analysis and visualization using Biovia Discovery Studio [11] and PyMol [18] in understanding their residual interaction.

Moreover, the protein was also docked with the first-line drugs commonly used against tuberculosis. The interaction analyses of these drug compounds were used as a control for the study to compare the result of the interaction of protein and phytochemicals. To provide enough space for free movements of the ligands, blind docking was performed where the grid box was constructed to cover the whole receptor. The grid points for the selected phytochemicals in the bark of *Syzygium cordatum* against 4RHT were set to 26 × 73 × 27, at a grid center of (x, y, z) 59.610, 45.268, 54.651 with a spacing of 1 Å. For common drugs against 4RHT, the grid points were set to 27 × 72 × 25, at a grid center of (x, y, z) 65.878, 45.887, 56.166 with a spacing of 1 Å. After the docking simulation was carried out, equations 1 and 2 were used in calculating the inhibition constants and inhibitory efficiencies of the docked ligands and drug compounds. The inhibition constant indicates how potent an inhibitor is; it is the concentration required to produce half maximum inhibition. Biovia discovery studio [11] and PyMol [18] were used to visualize and analyze the docking outputs.

$$Ki = e^{\left[\frac{\Delta G}{RT}\right]}. \quad (1)$$

Where R = Gas constant (1.987×10^{-3} kcal $mol^{-1}K^{-1}$); T=298.15 K (absolute temperature); K_i=Inhibition constant; ΔG_{bind}= Binding energy.

NOTE: AutoDock used binding energy to calculate inhibition constant. The binding energy is the free energy change for the protein-inhibition interaction ΔG is used to calculate the constant inhibition k_i,(*Equation 1*), which is the dissociation constant (k_d).

Results and Discussion

Molecular docking analysis

The binding affinities of all the docked 18 ligands and 4 first-line drugs used against 4RHT are shown in Table 1, which reflects their binding interaction with MtHGPRTrase. Based on the docking score, it is evident that all the ligands interact better with 4RHT than all the selected commonly used drugs except Rifampicin. Twenty-four [24] compounds were docked, sixteen of eighteen active compounds in the bark of S. cordatum plant as an anti-tubercular agent passed Pfizer's rule of five/Lipinski thumb rule [18] alongside four other common drugs considered for this study. Ten ligands showed excellent binding affinity ($\Delta G_{bind} \leq -7.2$) with (4RHT); these compounds are Epifriedelinol, Hesperidin, Friedelin, Arjunolic acid, Cyanidin, Delphinidin, Ellagic acid. Epigallocatechin, Leucocyanidin, Leucodelphinidin, and Tannin. It was also found that five compounds have a strong interaction ($\Delta G_{bind} \leq -8.0$) with the tuberculosis protein (4RHT); these are Epifriedelinol, Hesperidin, Friedelin, Arjunolic acid, and Tannin. Whereas the selected common drugs also interacted with the tuberculosis protein, still, they were not as good as the ligands except Rifampicin, which has a good binding affinity ($\Delta G_{bind} = -7.9$), but not as outstanding as those five ligands having strong interaction of $\Delta G_{bind} \leq -8.0$. Hence, this shows their outstanding inhibitory activity because higher binding affinity gives a corresponding

lower inhibition constant (K_i) as depicted in Table 1. The hit compounds among the docked ligands were further analyzed using ADMET [25].

Table 1. Binding Affinities and inhibition constant of the ligands and four first-line drugs

S/N	Ligands	Binding affinity (kcal/mol)	Inhibition constant (K_i) (μM)
1	Arjunolic acid	-8.2	0.98
2	Caffeic acid	-5.8	56.0
3	Cinnamic acid	-5.6	78.69
4	Cyanidin	-7.7	2.27
5	Delphinidin	-7.5	3.18
6	Ellagic acid	-7.3	4.45
7	Epifriedelanol	-8.9	0.30
8	Epigallocatechin	-7.2	5.27
9	Friedelin	-8.8	0.55
10	Gallic acid	-5.2	153.78
11	Glucose	-5.0	216.05
12	Hesperidin	-8.9	0.30
13	Hexahydroxydiphenic acid	-6.6	14.50
14	Leucocyanidin	-7.2	5.27
15	Leucodelphinidin	-7.2	5.27
16	P-coumaric	-6.0	39.95
17	Sinapic acid	-5.3	129.74
18	Tannin	-8.1	1.16
	First-line drugs		
1	Ethambutol	-4.5	502.50
2	Isoniazid	-4.7	358.53
3	Pyrazinamide	-4.4	594.90
4	Rifampicin	-7.9	1.62

Pharmacokinetic study analysis

Assessment of pharmacokinetic properties (ADME/T) helps predict the active compound's potential behavior in becoming a drugable candidate. This is important in drug discovery. A proposed therapeutic drug must obey Lipinski's rule [19] with not more than one (1) violation; Veber's rule [20] with at least two parameters satisfied as an effective and suitable drug candidate. ADMET properties of the selected compounds were predicted using the ADMET SAR2 webserver [21] and swissADME web server [22]. At the same time, drug-like features were evaluated using Molinspiration software, as shown in Tables 2 and 3. It is evident from the table that only two of the 18 selected ligands had more than one violation of the 'rule of five', which implies that a more significant percentage of the Ligands are of good oral bioavailability and permeability. Only two ligands of the selected hits and Rifampicin (C-4) had poor drug-like properties with more than 1 violation. This result revealed that all the selected hits except (L-12 and L-18) possessed excellent drug-like properties and could be developed further as oral drugs. Considering the binding affinities and inhibition constants (Table 1) which are expected to be within (0.1 μM and 1.0 μM), only four (4) of the docked compounds qualified as hits. However, when subjected to ADMET analysis using ADMET SAR-2 webserver [21, 26]. Notably, only Arjunolic acid, Caffeic acid, cinnamic acid, Epifriedelinol, Friedelin, Hexahydroxydiphenic acid, and sinapic acid (coded L-1, L-2, L-3, L-7,L-9, L-13, and L-17, respectively) showed excellent ADMET profile as discussed in Table 3, and they were selected for further analyses. Although Hesperidin and

Tannin had better inhibitory activities and binding affinities as Arjunolic acid, Friedelin, and Epifriedelinol, they were shunned based on not being orally available for humans.

Table 2. Drug-likeness of selected hit ligands and standards

Hit compounds	Code	Binding affinity (kcal/mol)	M/weight	log P	HBA	HBD	Rot bonds	No of violation	K_i (μM)
Arjunolic acid	L-1	-8.2	488.71	4.63	4	5	2	0	0.98
Caffeic acid	L-2	-5.8	180.16	0.94	3	4	2	0	56.27
Cinnamic acid	L-3	-5.6	148.16	1.91	1	2	2	0	78.85
Epifriedelinol	L-7	-8.9	428.75	8.04	1	1	0	1	0.3
Friedelin	L-9	-8.8	426.73	7.85	0	1	0	1	0.36
Hexahydroxydiphenic acid	L-13	-6.6	338.22	0.67	8	10	3	1	14.59
Sinapic acid	L-17	-5.3	224.21	1.51	4	2	4	0	130.8
First-line drugs									
Ethambutol	SD-1	-4.7	204.31	0.35	4	4	9	0	502.50
Isoniazid	SD-2	-4.5	137.14	-0.97	3	4	1	0	358.53
Pyrazinamide	SD-3	-4.4	123.11	-0.71	4	2	1	0	594.90
Rifampicin	SD-4	-7.9	822.9	2.62	16	6	5	3	1.62

Rot Bond = Rotable Bonds (any single non-ring bond attached to a non-terminal non-hydrogen atom)
log P is the partition coefficient or lipophilicity of the ligand and was determined using Molinspiration webserver (www.molinspiration.com).

Table 3. ADMET prediction of the selected hit ligands and standards

Absorption and distribution	L-1	L-2	L-3	L-7	L-9	L-13	L-17
BBB+/-	+0.9077	-0.4365	+0.9747	+0.9566	+0.9930	-0.6126	-0.3286
HIA +	+0.9486	+0.9645	+0.9718	+0.9885	+0.9858	+0.9802	+0.9619
Log S	-3.756	-1.694	-2.417	-3.968	-3.997	-2.485	-2.267
Human oral bioavailability	+0.5143	+0.6429	+0.6143	+0.5857	+0.6857	+0.8143	-0.6000
Metabolism							
CYP450 2C19	-0.9006	-0.9367	-0.9724	-0.8232	-0.8551	-0.9735	-0.9442
CYP450 1A2	-0.9008	-0.9046	-0.8383	-0.6354	-0.8321	-0.8771	-0.9282
CYP450 3A4	-0.9038	-0.8869	-0.9702	-0.9032	-0.9148	-0.8694	-0.9392
CYP450 2C9	-0.8439	-0.9071	-0.9763	-0.7446	-0.8329	-0.6877	-0.9390
CYP450 2D6	-0.9447	-0.9525	-0.9546	-0.9685	-0.9726	-0.9521	-0.9600
CYP inhibitory Promiscuity	-0.9508	-0.9007	-0.9687	-0.9411	-0.9530	-0.8780	+0.9863
Excretion							
Biodegradation	-0.8250	-0.5500	+0.7500	-0.7500	-0.8250	-0.8500	-0.8500
Toxicity							
Carcinogenicity	-1.0000	-0.8016	-0.7571	-0.9000	-0.8571	-0.6626	-0.8298
AMES Mutagenesis	-0.9300	-0.9100	-0.9000	-0.8000	-0.8000	-0.8900	-0.7300
hERG inhibition	-0.4853	-0.9044	-0.8459	-0.5511	-0.3925	-0.8092	+0.7297
Eye corrosion	-0.9930	-0.6303	+0.9052	-0.9532	-0.9212	-0.9961	-0.9926
Eye irritation	-0.9204	+1.0000	+1.0000	-0.8548	-0.8523	+0.9593	-0.8921
Acute oral Toxicity	III, 0.8032	IV,0.5588	III,0.8487	III,0.8644	III,0.7801	III, 0.6529	III, 0.8245

Oral bioavailability of the selected hit compounds and standards

Using the swissADME [22, 27] online tool, the oral-bioavailability profile of the selected hit ligands and standards were obtained and shown in Table 4. Figure 2 reveals a glimpse of the oral-bioavailability profile of the selected hits and standard drug. The optimum zones of each property are shown in pink on the radar, i.e., (FLEX, SIZE LIPO, POLAR, INSATU, and INSOLU). All the selected hits shown in Table 2 obeyed the recommended 500gmol^{-1} as suggested by the Lipinski rule, compared to 822.9 gmol^{-1} reported for Rifampicin. The selected hits' Total Polarity Surface Area (TPSA) depicts their polarity (POLAR). A polar compound is expected to have a TPSA value between 20 and 130 Å^2. The TPSA of L-1, L-2, L-3, L-7, and L-17 is within the acceptable scope, while L-9 and L-13 have lower and higher TPSA values, respectively, compared to the considerable value obtained for SD-4. However, SD-1, SD-2 and SD-3 have the best TPSA values; thus have the highest POLARITY property. AS REVEALED BY THEIR ESOL (LOGS), the INSOLU (insolubility) of the selected compounds and standards showed that L-1 is very soluble; L-3, L-13, and L-17 are moderately soluble; L-1, L-7, L-9, and C-4 have poor solubility. Remarkably, L-2 has the most outstanding ESOL (Log S) (− 1.89) and the highest aqueous solubility property among the selected hit compounds and standards. The number of the rotatable bond and Sp3 carbons (CSP3) is suggested to be ≤ 9 (Rotatable bonds) and within the range of 0.5–1 (CSP3) respectively. These are used to assess the unsaturation (INSATU) and flexibility (FLEX) of the selected hits and standards. Interestingly, CSP3 values of all the selected hits and Standards are within the acceptable range. The numbers of rotatable bonds in all the selected hits were not up to nine (9) as compared to SD-1 with the highest number of 9. xLogP3 and ESOL (Log S) with the suggested range of (− 0.7 and+5.0), and (0 and 6) respectively were used to access the Lipophilicity (LIPO) and Insolubility (INSOLU) profile of the selected hits and standards. Excluding L-1, L-7, L-9, and C-4, the xLogP3 and ESOL (Log S) of all the selected hits and standard drugs are within the recommended range. All the selected hits and standards could be explored further in search for a promising anti-tubercular agent as seen orally available.

Bioactivity, Binding mode and Molecular interactions of the selected hits and standards

The ratio of binding energy per non-hydrogen atom is determined by Ligand efficiency. The Inhibition constant (Ki) is used in calculating the Ligand efficiency, which shows the dissociation constant and bond strength between the ligand/protein [23,24]. The most potent inhibitors Acyclic Nucleoside Phosphates (ANPs), have K_i values of 0.69 and 0.77 μM, with both having guanine as the base [15]. Low values indicate the strong binding of the molecule to the protein. Thus, ligands with relatively low values were considered. Equations 2 and 3 are used in calculating K_d/K_i and LE

$$\Delta G_{bind} = -2.303RT \log(K_i) \quad (2)$$

$$K_i = \mathrm{Exp}\,(\Delta G_{bind}/RT) \quad (3)$$

$$LE = \frac{-2.303RT}{HAC} \log(K_i) \quad (4)$$

$\Delta G_{bind}$is the binding energy (kcal mol^{-1}) [17,28] gotten from docking scores, R is the gas constant with value1.987 × 10^{-3} kcalmol^{-1}K^{-1} and T is the temperature at 298.15 K standard conditions. The affinity of the ligands and that of the first-line drugs docked to the MtHGPRTrase were compared using the dissociation constant (K_d) and ligand efficiency (LE). Low values of these parameters indicate that the Ligands/drug compounds bond closely to the protein. LE gives the average binding energy per non-hydrogen atom. Table 5 shows the values allowing the

comparison of the selected ligands with standard drugs. Three of the seven selected best ligands obtained from the pharmacokinetic study and one standard drug (Rifampicin) exhibit low K_i values, concluding that these ligands and the drug have good binding interactions. Based on this, L-1, L-7, and L-9 are excellent prospects to be used as MtHGPRTrase inhibitors, whereas others with favorable LE values and few liabilities can also be explored.

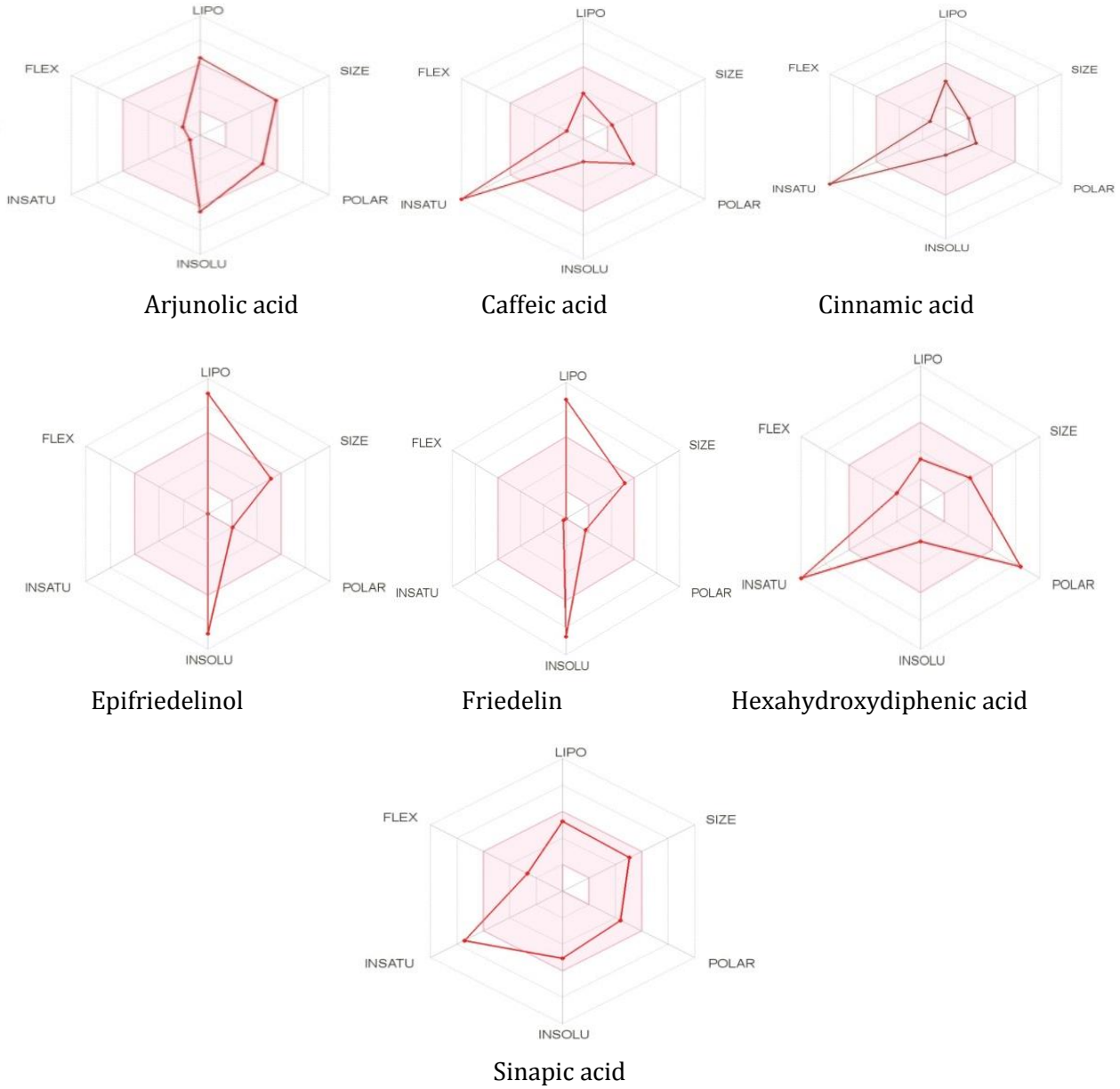


Figure 4. Bioavailability radar of the selected hit ligands

L-1 formed a conventional hydrogen bond with Gly67, Val64, and Lys137; and residue interactions with Val64, Leu65, Lys66, Ala68, Asp123, Val124, Asp126, Thr130, Lys 154 Phe175, Val176, Val177, Leu181, Asp182, and Tyr183. L-7 formed a conventional hydrogen bond with Lys66, Gly67, and residue interactions with Leu65, Asp123, Val124, Lys154, Asp174, Phe175, Val176, Asp182, and Arg188. L-9 formed only a residue interaction with Val64, Val90,

Glu122, Asp123, Val124, Thr130, Lys154, Asp174, Phe175, Val176, Leu181, and Asp182 as demonstrated in Table 5. Interestingly, L-1 and L-7 held a hydrogen Bond with Gly67, and (Gly67, Lys66) respectively as GMP.PPi complex did in the product binding [13]. Notably, all the selected ligands except L-13 formed a residue interaction with Phe175 as GMP.PPi complex did in the binding of the product. Only Pyrazinamide of all the four first-line drugs formed hydrogen bonds with Lys66 and Gly67 while only Ethambutol formed a residue interaction with Phe175 as GMP.PPi complex did in the binding of the product. Comparing binding energies, binding poses, and pharmacokinetic properties of the selected ligands and the prescribed first-line drugs shows there is promising lead(s) for the treatment of tuberculosis in the bark of *Syzygium cordatum,* which could be explored and developed by medicinal chemists and pharmaceutical companies as a better anti-tubercular agent

Table 4. The oral bioavailability of the selected hits and standard

Ligand/ standard drugs	L-1	L-2	L-3	L-7	L-9	L-13	L-17	SD-1	SD-2	SD-3	SD-4
Formula	$C_{30}H_{48}O_5$	$C_9H_8O_2$	$C_{15}H_{11}O_6$	$C_{15}H_{14}O_7$	$C_7H_6O_5$	$C_{15}H_{14}O_7$	$C_{11}H_{12}O_5$	$C_{10}H_{24}N_2O_2$	$C_6H_7N_3O$	$C_5H_5N_3O$	$C_{43}H_{58}N_4O_{12}$
Mass	488.71	180.16	148.16	428.75	426.73	338.22	224.21	204.31	137.14	123.11	822.9
Vina Score	-8.2	-5.8	-5.6	-8.9	-8.8	-6.6	-5.3	-4.5	-4.7	-4.4	-7.9
TPSA (A2)	97.99	77.76	37.30	20.23	17.07	195.98	75.99	64.52	68.01	68.87	220.15
No. of Rotatable bonds	2	2	2	0	0	3	4	9	2	1	5
XLOGP3	5.84	1.15	2.13	10.08	9.80	0.47	1.46	-0.08	-0.70	-0.60	5.46
WLOGP	5.18	1.09	1.68	8.25	8.46	0.98	1.40	-0.29	-0.31	-0.42	3.00
ESOL LogS	-6.42	-1.89	-2.37	-8.85	-8.66	-2.41	-2.16	-0.46	-0.56	-0.65	-8.18
ESOL CLASS	Poorly soluble	Very soluble	Poorly soluble	Poorly soluble	Soluble	soluble	soluble	Very soluble	Very soluble	Very soluble	Poorly soluble
Lipinski violations	0	0	0	1	1	1	0	0	0	0	3
Bioavailability score	0.56	0.56	0.85	0.55	0.55	0.11	0.56	0.55	0.55	0.55	0.17
PAIN alerts	0	1	0	0	0	1	0	0	0	0	3
Fraction Csp3	0.90	0.00	0.00	1.00	0.97	0.00	0.18	1.00	0.00	0.00	0.53
Synthetic Accessibility	6.45	1.81	1.67	5.27	5.17	2.62	2.17	2.40	1.24	1.47	9.23
Heavy atoms	35	13	11	31	31	24	16	14	10	9	59

Table 5. Binding interaction of the selected hit ligands and standards

Ligands/ standard drugs	Binding Affinity (kcal/mol)	Binding interaction		Ligand Efficiency	
		Hydrogen Bond	Residue interactions	K_d/k_i	LE (kcal/mol)
L-1	-8.2	Val64, Gly67	Val64, Leu65, Lys66, Ala68, Asp123, Val124, Asp126, Thr130, Lys154 Phe175, Val176, Val177, Leu181, Asp182, Tyr183	0.97 x10^{-6}	0.234
L-2	-5.8	-	Phe175,Val176,Val177, Tyr183, Leu196, Asp197, Pro198	55.99x 10^{-6}	0.446
L-3	-5.6	Val176, Asp182	Phe175, Val177, Tyr183, Leu196, Pro198	78.48x10^{-6}	0.509
L-7	-8.9	Lys66, Gly67	Leu65, Asp123, Val124, Lys154, Asp174, Phe175, Val176, Asp182, Arg188	0.30 x10^{-6}	0.287
L-9	-8.8	-	Val64, Val90, Val124, Glu122, Asp123, Thr130, Lys154, Asp174, Phe175, Val176, Leu181, Asp182	0.35 x10^{-6}	0.284
L-13	-6.6	Glu122, Asp123, Val124, Asp126, Gly128	Val64, Val125, Leu129, Leu131, Thr130, Leu181	14.51x10^{-6}	0.275
L-17	-5.3	Asp126, Lys154, Val176	Val124, Val125, Gly128, Asp174 Phe175, Val177, Leu181, Asp182	130.21x10^{-6}	0.331
SD-1	-4.5	-	Val124, Lys154, Asp174, Phe175, Val176, Val177, Leu181, Asp182, Tyr183, Leu196	502.50x10^{-6}	0.321
SD-2	-4.7	Val176, Asp182	Val124, Lys154, Asp174, Phe175, Val177, Leu181, Tyr183, Leu196	358.53x10^{-6}	0.470
SD-3	-4.4	Leu65, Lys66, Gls67 Asp182, Arg188	Val64, Asp123, Glu122	594.90x10^{-6}	0.489
SD-4	-7.9	Val176	Val64, Lys66, Val90, Ser91, Ser92, Val103, Glu122, Asp123, Val124, Thr130, Lys154, Val177, Leu181, Asp182, Tyr183, Asp184, Arg188,	1.62 x10^{-6}	0.134

Figure 5. Binding mode and molecular interactions of the selected hits and standards

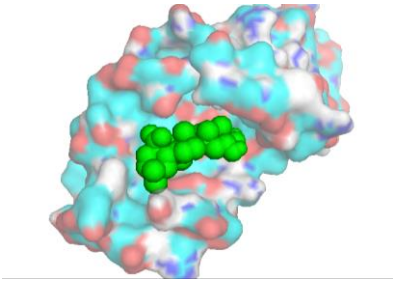
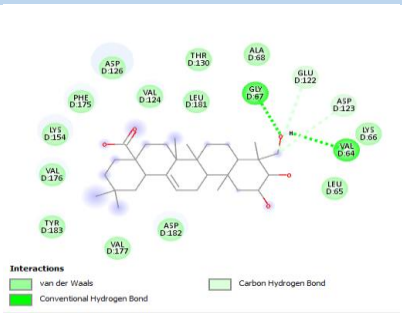
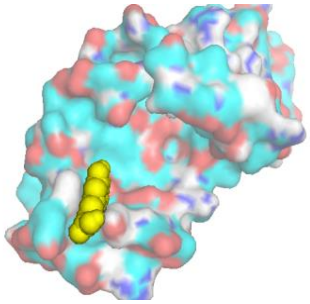
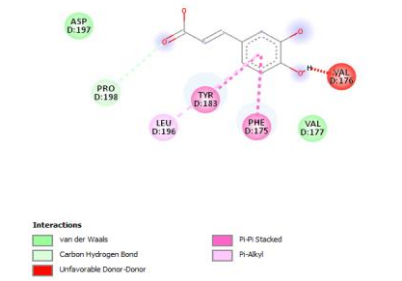
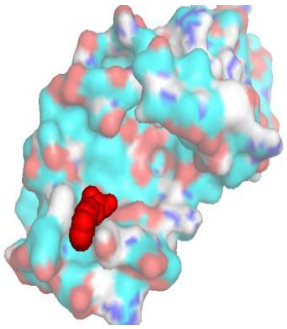
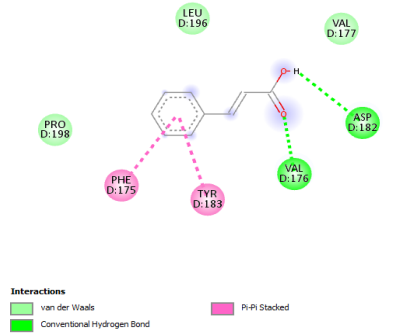
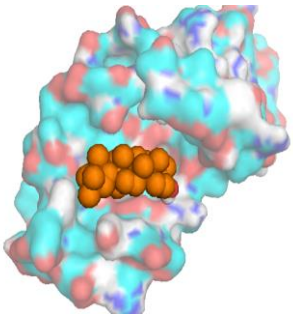
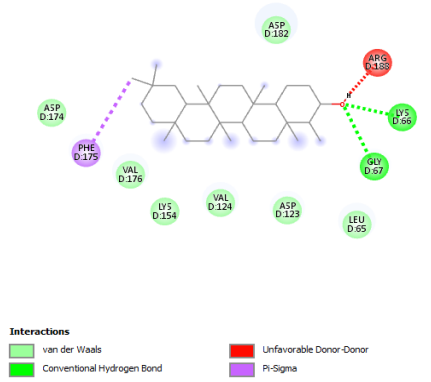
Ligands/standard drugs	3D	2D
Arjunolic acid		
Caffeic acid		
Cinnamic acid		
Epifriedelinol		

Figure 5. Continued

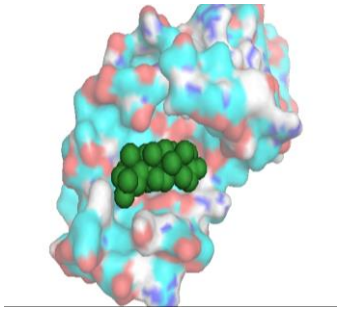
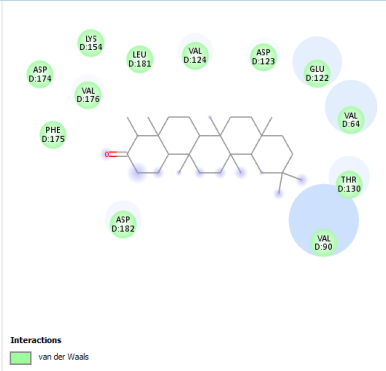
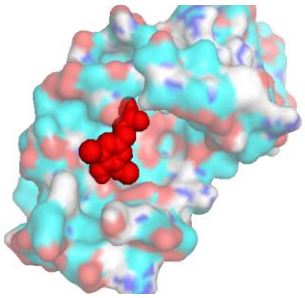
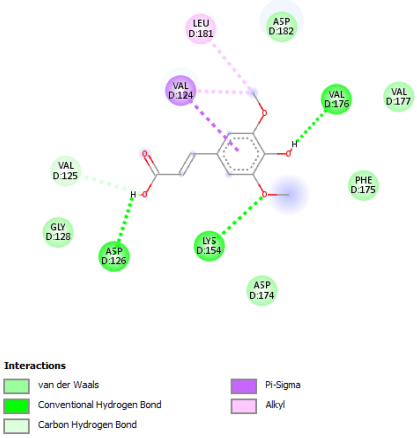
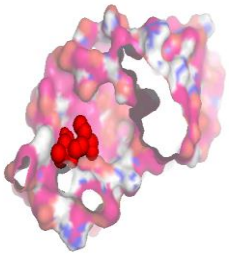
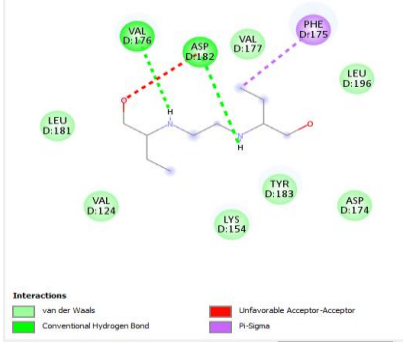
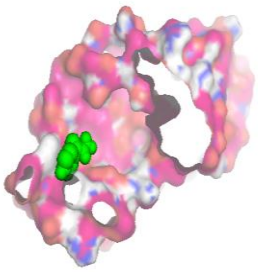
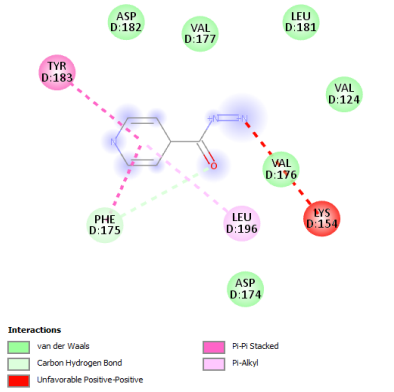
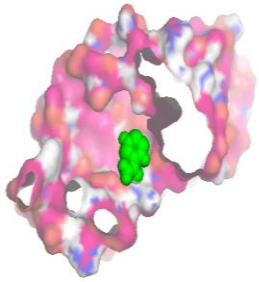
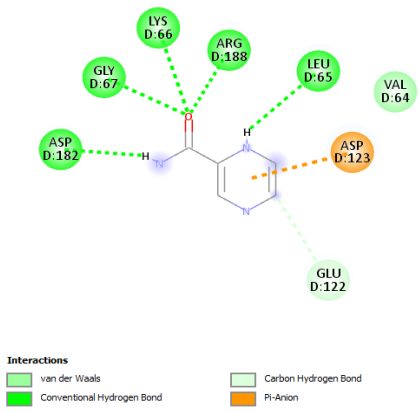
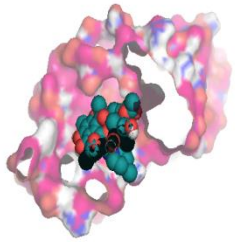
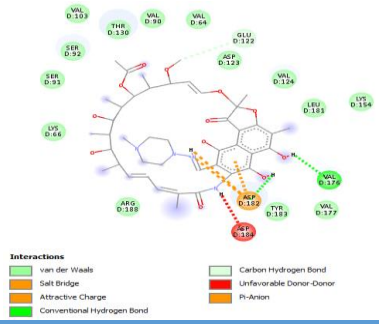
Ligands/standard drugs	3D	2D
Friedelin		
Sinapic acid		
Ethambutol		
Isoniazid		

Figure 5. Continued

Ligands/standard drugs	3D	2D
Pyrazinamide		
Rifampicin		

Conclusion

This research compares the theoretical evaluation of the compounds derived from the bark of *Syzygium cordatum* and the four First-line drugs through a molecular docking approach. This approach was used to identify the most promising candidates that may inhibit the MtHGPRTrase of the *Mycobacterium tuberculosis.* Also, a pharmacokinetics study was carried out to justify the potency of these ligands. It was observed that quite a number of the phytochemicals have good binding affinities much better than synthetic drugs. Seven compounds (Arjunolic acid, Caffeic acid, Cinnamic acid, Epifriedelinol, Friedelin, Hexahydroxydiphenic acid, and Sinapic acid) were identified among the screened ligands as potential inhibitors of *Mycobacterium tuberculosis* (4RHT) because they exhibit better molecular interactions, binding mode, and pharmacochemical properties. This study thereby recommends 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) as potential inhibitors of Mycobacterium tuberculosis (4RHT) with better pharmacokinetics and bioavailability and thereby recommended for therapeutic efficacy investigation and adoption to join the existing drugs for tuberculosis.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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