

ANTITUBERCULOSIS POTENTIAL OF *Caesalpinia sappan* BIOACTIVE COMPOUNDS USING IN SILICO APPROACH

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Received: 24 July 2025 | Revised: 18 October 2025 | Accepted: 22 November 2025 | Published: 30 April 2026
UPT Publication and Journal Management Uniska-JST 2026

Abstract *Caesalpinia sappan* has been reported to possess a plethora of pharmacological effects, including immunomodulatory, antibacterial, astringent, and antitumor properties. The present study set out to ascertain the benefits of the active compounds *Caesalpinia sappan* in terms of their ability to inhibit the action of the Arabinosyltransferase C enzyme in *M. tuberculosis*. This research was conducted using an in-silico approach with the following applications: PyMOL, PyRx, AutoDock 4, Biovia Discovery Studio, and Toxtree. The results demonstrated that among the 25 test compounds, gallic acid exhibited the highest Pa value. The gallic acid compound has been found to have the lowest ΔG free bond energy (-7.0 kcal/mol), which is lower than the native ligand and has more hydrogen bonds than the ethambutol. Consequently, gallic acid compounds can impede the function of the Arabinosyl Transferase C receptor.

Keywords: Molecular Docking •
Antituberculosis • Natural
Compounds • Sappan wood



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Introduction

Caesalpinia sappan is a medicinal plant that is widely consumed throughout Asia. In Indonesia, the consumption of sappan wood is traditionally associated with the preparation of an herbal drink, which is known by various local names. The addition of slices of *Caesalpinia sappan* wood to boiling water results in a colour change of the water to a reddish hue. This process indicates the completion of the scalding process, and the water is then ready for consumption. The boiled water has been demonstrated to possess immunomodulatory, antibacterial, astringent, and antitumour properties. The reddish hue exhibited is contingent on the pH level of the water (Vardhani, 2019; Intan & Silvia, 2021).

Caesalpinia sappan has been reported to contain homoisoflavonoid and phenolic compounds, including 4-O-methylsappanol, protosappanin A, protosappanin B, protosappanin E, brazilin, brazilin, and caesalpin. *Caesalpinia sappan* is a plant that has been shown to possess significant health and cosmetic benefits. Empirical evidence has demonstrated its efficacy in healing various infectious diseases caused by bacteria (Intan & Silvia, 2021; Aisya et al., 2023).

Tuberculosis is an infectious disease. It is caused by *Mycobacterium tuberculosis*. Tuberculosis (TB) is a disease that is responsible for a significant proportion of population mortality, especially in developing countries such as Indonesia. The global prevalence of *Mycobacterium tuberculosis* has been estimated to be approximately one-third of the global population. It is estimated that 11% of all tuberculosis cases occur in children under the age of 15. The prevention and treatment of

tuberculosis necessitate a relatively protracted period. Nevertheless, it has been demonstrated that not all patients infected with tuberculosis are cured through standard treatment (Ruswanto, 2015; Ningrat, 2022).

The standardised treatment for tuberculosis (TB) involves a combination of four anti-tuberculosis medications: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). The proteins located in the cell membrane of *M. tuberculosis* are targeted in TB treatment. The proteins have been identified as rabinosyltransferase C Enzyme and Enoil asil carrier protein reductase (InhA). Arabinosyltransferase C enzyme has been identified as the catalyst for the addition of arabinose groups to arabinogalactan. Arabinogalactan constitutes a significant and indispensable component of the cell wall of *Mycobacterium*. The development of resistance to antituberculosis drugs can be attributed to mutations in the *Mycobacterium tuberculosis* genes. Research into antituberculosis drugs is driven by the emergence of resistance. Mutations in *Mycobacterium tuberculosis* genes result in resistance to antituberculosis drugs. These mutations result in alterations to the protein structure, which is the target of the drug, thereby compromising its effectiveness. Indonesia is currently one of the countries with a high burden of drug-resistant tuberculosis (TB) in the world, especially multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). MDR-TB is characterised by its resistance to isoniazid and rifampicin, and the potential to also demonstrate resistance to other tuberculosis (TB) medications. Meanwhile, XDR-TB has been observed to demonstrate resistance to second-line TB drugs. The emergence of resistance to TB drug medications necessitates the identification and development of novel therapeutic agents to combat this resistance (Rinanda, 2015; Lailiyyah et al., 2023 Fiona et al., 2024).

In silico is a technique that can be used in the process of drug discovery, especially for compounds in traditional plants that have no known activity. The Lipinski Rule of Five test is

a method that can be used to determine whether a drug candidate compound is drug-like. Molecular docking is a method used to identify interactions between receptor and ligand molecules by computation. This technique can be used as a reference and combined with in vitro and in vivo studies in drug discovery. The merits of this technique are evident in its efficiency in terms of the period and financial resources it demands. The parameters used were binding affinity and residue similarity between the native ligand and the test ligand. The strength of the bond between the ligand and the receptor increases as the binding affinity value decreases. Residue similarity is defined as the degree to which the test ligand is similar to the native ligand in terms of binding to the protein (Endriyatno, 2022; Lailiyyah et al., 2023).

The emergence of resistance to tuberculosis (TB) drugs has become one of the major challenges in global TB control. This situation necessitates the identification and development of new drug candidates with improved effectiveness. One promising approach is the exploration of herbal plants as sources of bioactive antituberculosis compounds. Sappan wood *C. sappan* traditionally known for its various medicinal properties, is one of the plants of particular interest. Although sappan wood has been widely studied for several pharmacological activities, no research to date has specifically evaluated its antituberculosis potential. This gap highlights the need for further scientific investigation to assess its viability as a novel antituberculosis candidate. An initial strategy to explore this potential is through in silico techniques, which enable rapid and efficient evaluation of bioactive compound interactions with tuberculosis molecular targets

Materials and Methods

The research was conducted using an Axioo MyBook Pro K3 PC device, which is equipped with an 11th Gen Intel(R) Core(TM) i3-1115G4 @ 3.00GHz 3.00 GHz processor, 238 GB storage, 8.00 GB RAM, and a 64-bit operating system. The software and web server utilised in this

research include PyMOL 2.6, PyRx, Biovia Discovery Studio 2021, ToxTree, KnapSack, PASS (Prediction of Activity Spectra for Substances), Pubchem, PDB, SWISSADME, and PreADMET.

The materials used in this study were the 3D structure of the Arabinosyltransferase enzyme, ethambutol, and *Caesalpinia sappan* bioactive compounds. The research methodology employed in this study comprises the following:

1. Preparation of bioactive compounds. The bioactive compounds of *Caesalpinia sappan* have been identified on the KnapSack database (<https://www.knapsackfamily.com>)
2. Potential prediction of compounds. The potency of the compounds was predicted using the PASS online website. (<https://www.way2drug.com/passonline/>)
3. 3D structures of receptors and ligands preparation. The 3D structure of the receptor has been downloaded from the Protein Data Bank (PDB; <https://www.rcsb.org>), and the 3D compounds have been downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov>)
4. Drug-likeness test. The drug-likeness test was performed to characterize the physicochemical profile of the compound to determine its ability as an oral drug. The test was conducted on the SwissADME website (<http://www.swissadme.ch/index.php>). Parameters used were molecular weight, logP, molar refractivity, hydrogen bond donors, and hydrogen bond acceptors.
5. Preparation of receptors and ligands. The 3D structure of the receptor was prepared by the removal of water and amino acid residues on Biovia Discovery. The preparation of the test ligand and comparison ligand is achieved by minimizing them in PyMol software.
6. Molecular Docking. The validation of the docking method (receptor-native ligand) and molecular docking (receptor-test ligand; receptor-comparison ligand) was conducted using PyRX Autodock software.
7. Analysis and Visualization. Analysis and visualization of simulation results on PyRx

and Biovia Discovery Studio 2021 software, both in 2D and 3D.

8. ADMET analysis on the PreADMET website (<https://preadmet.webservice.bmdrc.org>) and ToxTree software

Results and Discussion

Prediction of Potential Compounds

A total of 25 compounds in *C. sappan* were obtained from the KnapSack website. Prediction compound potency aims to establish a comprehensive understanding of the properties and biological activity of these compounds, with a particular focus on their application as pharmaceutical agents. The parameters employed in this study are Pa (Potential Activity) and Pi (Potential Inactivity) values. The prediction of the potential of plant compounds is facilitated by the online platform, way2drug PASS. The analysis of the potential of *C. sappan* compounds as antibacterial can be seen in Table 1. Based on Table 1, It can be seen that the Gallic acid compound has a higher Pa value (0.418) than the other 24 compounds. The following compounds were identified: Phanginin F (0.387); Ombuin (0.362); Sappanchalcone (0.333); Isoliquiritigenin 2'-methy ether (0.324); 2'-Methoxyisoliquiritigenin (0.324); Phanginin B (0.309); and Phanginin G (0.305).

The online PASS test results provide information related to Pa (Potential activity) and Pi (Potential inactivity) values. The compound was expected to demonstrate activity if the Pa value exceeded the Pi value. When the Pa value exceeds 0.7, it is considered to be sufficiently elevated for experimental purposes and possesses drug-like activity. If the Pa value of the compound is between 0.7 and 0.5, then the compound is considered to be relatively low in experimental value. Whereas, if the Pa value of the compound is below 0.5, then the compound is experimentally very small (Nurfadillah et al., 2025).

Drug-Likeness Test

The drug-likeness test is a method used to predict a molecule or compound's permeability and

absorption properties of the 25 *C. Sappan* plant compounds, only 1 was selected for the drug-likeness test. This is because only 1 compound has a relatively high Pa value compared to 24 other compounds. The results of the drug-likeness of the test compound and native AFO ligand can be seen in Table 2. Five parameters must be met, namely: Mass <500 D, Hydrogen Bound Donors (HBD) not more than 5, Hydrogen Bound Acceptors (HBA) not more than 10, LogP not

more than 5, and Molar Refractivity between 40-130. Based on Table 2, it can be seen that the test compounds have smaller Mass, LogP, and MR values than the native ligand. The drug is expected to be able to reach the target so that the active compounds contained in the drug can interact well in the body. A drug given orally must fulfill the five rules; otherwise, it is better given by injection because it is thought to harm the human body (Nurfadillah et al., 2025).

Table 1. Pa and Pi values of *C. sappan* compounds as antibacterials

No	Compounds	Formula	Pa Value	Pi value
1	Ombuin	C ₁₇ H ₁₄ O ₇	0,362	0,040
2	Gallic acid	C ₇ H ₆ O ₅	0,418	0,026
3	Sappanchalcone	C ₁₆ H ₁₄ O ₅	0,333	0,048
4	Isoliquiritigenin 2'-methy ether	C ₁₆ H ₁₄ O ₄	0,324	0,052
5	Brazilin	C ₁₆ H ₁₄ O ₅	0,025	0,012
6	3'-Deoxysappanone B	C ₁₈ H ₁₈ O ₅	0,232	0,094
7	3'-O-Methylbrazilin	C ₁₇ H ₁₆ O ₅	0,096	0,086
8	8-Methoxybonducellin	C ₁₈ H ₁₆ O ₅	0,278	0,068
9	4-O-Methylsappanol	C ₁₇ H ₁₈ O ₆	0,237	0,091
10	Protosappanin E-2	C ₃₂ H ₂₆ O ₁₁	0,094	0,093
11	2'-Methoxyisoliquiritigenin	C ₁₆ H ₁₄ O ₄	0,324	0,052
12	4-O-Methyl episappanol	C ₁₇ H ₁₈ O ₆	0,237	0,091
13	3-deoxysappanone B	C ₁₆ H ₁₄ O ₅	0,215	0,104
14	Neosappanone A	C ₃₃ H ₂₈ O ₁₁	0,105	0,062
15	Phanginin A	C ₂₁ H ₂₈ O ₅	0,275	0,070
16	Phanginin B	C ₂₁ H ₂₈ O ₅	0,309	0,057
17	Phanginin C	C ₂₂ H ₃₀ O ₅	0,095	0,088
18	Phanginin D	C ₂₂ H ₃₀ O ₅	0,247	0,085
19	Phanginin E	C ₂₁ H ₂₆ O ₅	0,229	0,095
20	Phanginin F	C ₂₁ H ₂₈ O ₅	0,387	0,033
21	Phanginin G	C ₂₁ H ₂₈ O ₅	0,305	0,058
22	Phanginin H	C ₂₁ H ₂₈ O ₄	0,209	0,109
23	Phanginin I	C ₂₁ H ₂₈ O ₄	0,033	0,004
24	Phanginin J	C ₂₁ H ₂₆ O ₅	0,033	0,004
25	Phanginin K	C ₂₂ H ₂₈ O ₆	0,034	0,004

Source: Knapsack dan Way2Drug PASS online (2025)

Table 2. Results of the Drug likeness test for the compounds

No	Compound Code	Massa	HBD	HBA	LogP	MR
1.	Ligan AFO	262,3	3	5	0,80	68,15
2.	Gallic acid	170	4	5	0,50	39,47

Source: SwissADME (2025)

If the molecular mass is >500 Dalton, it will cause failure in the process of molecular diffusion through the cell membrane. Furthermore, a drug candidate molecule or compound must also have an HBD value of less than 5 and an HBA of less than 10, which is related to the energy of the absorption process. It has been demonstrated that the magnitude of the energy required for the absorption process is inversely proportional to the hydrogen bonding capacity. Furthermore, a drug molecule or compound must have a high lipophilic or LogP value ranging from -0.4 to 5. The LogP value is defined as the solubility coefficient in fat or water. The greater the log P value of a molecule, the more hydrophobic the compound is. But if the molecule has high hydrophobic properties, it will cause toxicity in the body. This is because the molecule is distributed more widely due to being stuck on the membrane for too long. Nevertheless, it is evident that the smaller the log P value, the less capable the molecule or drug compound is of penetrating the membrane (Maftucha et al., 2022). Gallic acid has met all five criteria, so it can be concluded that gallic acid has physicochemical properties that are suitable for oral medicine.

Molecular Docking

The ligand and receptor that have been prepared were then subjected to molecular docking simulations on Autodock software. Receptor preparation was done by removing water, residue, and native ligand. Removal of water molecules was done in order to maximize the interaction between the test ligand and the receptor. The interaction between ligand and receptor generally occurs through the formation of hydrogen bonds. Consequently, the addition of hydrogen is imperative to optimise this interaction. The preparation of the ligand was undertaken to enhance its stability during the molecular docking process. This was achieved by minimising the ligand (Nurfadillah et al., 2023). The following parameters were used: binding affinity, root mean square deviation (RMSD) value, bond type, amino acid residues formed, and bond distance. The results of the molecular docking are

presented in Table 3. Binding affinity is a parameter that indicates the strength of the interaction between the ligand and the receptor. As can be seen in Table 3, the binding affinity value of the test compound is smaller than the native ligand and the comparator ligand. The smaller the value, the stronger and more stable the bond formed between the ligand and the receptor. Negative values indicate the lowest energy required for the receptor to interact with the ligand so that the reaction can occur spontaneously (Nurfadillah et al., 2025).

The root mean square deviation (RMSD) is a parameter employed to facilitate the comparison of atomic positions between experimental and predicted structures. As seen in Table 3, it can be concluded that the test compound has an atomic position that matches the native ligand, as indicated by an RMSD value of 0. This aligns with the criteria for successful docking, which requires an RMSD value of less than $2.0 \text{ \AA}$. This indicates that the pose of the native ligand and the test compound is becoming more similar, as it is close to the conformation of the native ligand (Nurfadillah et al., 2023).

The interaction between the receptor and the ligand results in bonds, bond distances, and amino acid residues. The bonds that can occur in this interaction include hydrogen bonds, van der Waals bonds, and other types of bonds. Hydrogen bonds are stronger than van der Waals bonds because they can form despite the distance between the ligand and the receptor. The interaction between the receptor and the native ligand involves four hydrogen bonds. The interaction between the test compound and the receptor shows three hydrogen bonds, while the interaction between the comparison ligand and the receptor shows two bonds. The greater the number of hydrogen bonds, the more stable the ligand-receptor bond. Bond energy value shows the affinity (strength) of the ligand to the target protein. Smaller bond energy increases the potential for binding to the target protein, and the more hydrogen bonds formed, the greater the ligand's affinity (Allo et al., 2023).

Table 3. Molecular Docking results of ligands and Arabinosyltransferase C enzyme receptor

No	Compound	Binding Affinity (Kcal/mol)	RMSD	Amino Acid Residue	Hydrogen Bond	Bond Distance
1	AFO Ligand	-6.6	0	TRP926	TYR841	2,80
				ALA925	SER1047	2,76
				PRO840	ASN928	3,24
				THR1044	TRP1057	3,02
				VAL1045		
				TYR841		
				ALA1059		
				ALA1046		
				LEU1060		
				SER1047		
				ARG927		
				VAL920		
				ASN928		
				ARG930		
				TRP1057		
				GLY1058		
				ASP1056		
2	Gallic acid	-7.0	0	TYR841	SER1047	2,52
				ARG927	VAL1045	2,13
				ARG930	ASP1056	2,14
				ASN928		
				TYR1048		
				SER1047		
				ALA1046		
				VAL1045		
				LEU1060		
				THR1044		
				TRP1057		
				GLY1058		
				ASP1014		
				ASP1056		
				ALA1059		
3	Ethambutol	-4,9	0	TYR841	TYR841	1,95
				TRP1057	ASP1056	2,42
				SER1047		
				ASP1056		
				ALA1059		
				VAL920		

Table 4. Results of ADMET Gallic Acid analysis

No	Compound	Absorbtion		Distribution		Toxicity			
		Caco2	HIA	PPB	BBB	Pgp inhibition	Kroes TTC	Carsinogen	Mutagen
1	Gallic Acid	20.60	92.95	98.43	0,34	Inhibitor	Safe	-	-

Source: *Preadmet*; *Toxtree* (2025)

The observation of amino acid residues is used to identify ligand-receptor interactions. These interactions are more stable and effective between compounds with amino acid residues that form hydrogen bonds. In the interaction between the receptor and the native AFO ligand, there are four amino acid residues with hydrogen bonds, with distances ranging from 2.76 to 3.84 Å. In the interaction between the test compound and the receptor, there are three amino acid residues with hydrogen bonds, ranging in distance from 2.13 to 2.52 Å. For the interaction between the ethambutol comparator ligand and the receptor, two amino acid residues form hydrogen bonds with a distance range of 1.95–2.45 Å. In molecular docking, the ideal hydrogen bond distance usually ranges from 1.5 to 2.5 Å. Hydrogen bonding is an important non-covalent interaction that occurs when a hydrogen atom is bound to an electronegative atom, such as oxygen or nitrogen, and interacts with another electronegative atom (figure 1) (Makatita et al., 2020).

ADMET Analysis

The ideal drug candidate should display not only sufficient efficacy against the therapeutic target, but also appropriate ADMET properties at a therapeutic dose. ADMET analysis is used to investigate how drugs enter the cells. ADMET analysis consists of parameters relating to absorption, distribution, metabolism, and toxicity. Absorption parameters include HIA (human intestinal absorption) and Caco-2 (cancer colon-2). Distribution parameters include PPB (plasma protein binding) and BBB (blood-brain barrier). Metabolism parameters include CYP, while toxicity is assessed in terms of mutagens and carcinogens (Guan et al, 2018; Nurfadillah et al., 2025).

The HIA value indicates the degree to which the active substance is absorbed in the

human gut. There are three categories: HIA 0–20% (low), 20–70% (medium), and 70–100% (high). Based on Table 4, the test compound is classified as having medium absorption. Predicting drug absorption by the human gut (HIA%) is important in developing potential drug compounds. Absorption in the small intestine is a pivotal process in determining the bioavailability of drugs when administered orally. Caco-2 cell modelling is recommended for predicting the absorption of orally administered active substances. The uptake quality of Caco-2 cells is categorized into three groups: <4 (low), 4–70 (medium), and >70 (high). Based on Table 4, it can be concluded that the test compound is considered to have moderate permeability or uptake ability (Radchenko et al, 2016; Nurfadillah et al., 2025).

Good drug distribution requires effective BBB and PPB channeling capabilities. Table 4 shows that the test ligand has a PPB value of 98.43%. A %PPB value of more than 90% indicates that the compound is strongly bound to plasma proteins. The prediction of PPB affinity is a crucial step in the screening process of protein drugs. Therefore, an increase in the PPB affinity is indicative of a stronger binding interaction between the pharmaceutical compound and the receptor (Liu et al, 2024).

The BBB constitutes a natural protective membrane that prevents the central nervous system (CNS) from toxins and pathogens in the blood. The BBB value indicates the permeability of the tested drug across the blood-brain barrier. The BBB value is categorised into three based on the strength of absorption: high (>2), medium (2–0.1), and low (<0.1). Based on Table 4, it can be concluded that the test ligands were sufficiently able to cross the blood-brain barrier. However, not all drugs need to cross the blood-brain barrier if their target is not related to the central nervous system (Wu et al, 2023).

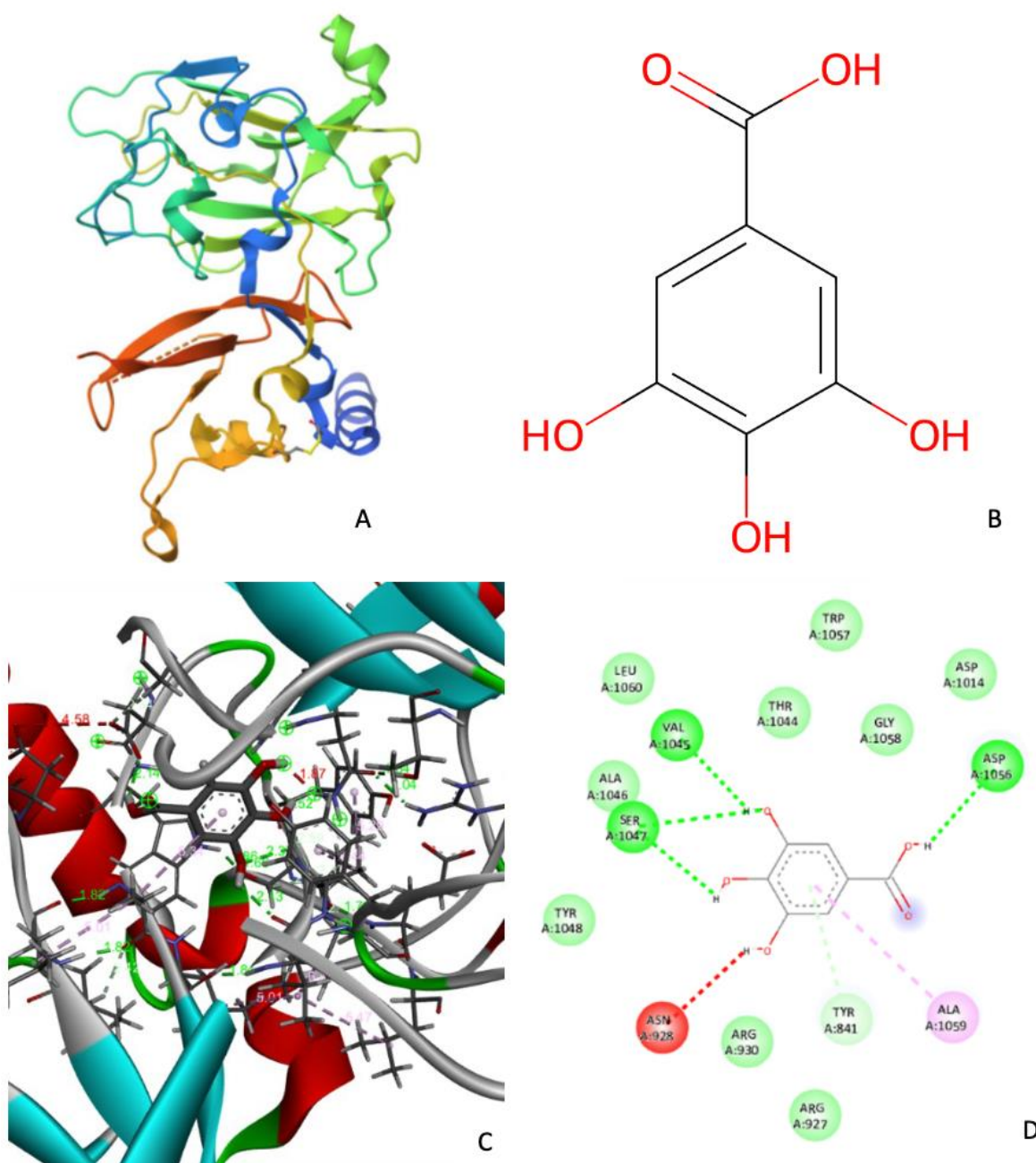


Figure 1. Molecular docking simulation: (A) 3D structure of arabinosyltransferase C enzyme receptor; (B) 2D structure of gallic acid test ligand; (C) 3D visualisation of interaction between receptor and gallic acid; (D) 2D visualisation of interaction between receptor and gallic acid, showing bond type and amino acid residues.

P-glycoprotein is a member of the ATP-binding cassette (ABC) superfamily and the best-characterized efflux transporter for drug discovery. P-gp demonstrates extensive substrate specificity and is expressed in the luminal

membrane of enterocytes and brain capillary endothelia, as well as the apical membrane of hepatocytes and kidney proximal tubule epithelia. P-gp plays a significant role in the processes of absorption, distribution, and excretion of drugs.

The impact of this mutation on the pharmacological and toxicological profile of P-gp substrates is a subject of considerable interest. Furthermore, P-gp inhibitors have been demonstrated to result in enhanced exposure and toxicity of P-gp substrates. It is imperative to ascertain the potential of novel pharmaceutical agents as P-gp substrates or inhibitors, to optimise pharmacokinetic profiles and predict drug-drug interactions (DDIs) in the context of drug discovery (Kido et al, 2024). Analysis indicates that gallic acid is an inhibitor of P-gp. This may cause an increase in the drug's

concentration within the cell, which could enhance the drug's therapeutic effect.

The evaluation of drug candidates for safe use necessitates the consideration of toxicity as one of the primary criteria. It is widely acknowledged that an early toxicity assessment is crucial in the context of drug discovery. It has a substantial impact on the attrition rate of candidates. The toxicity parameters used in this study are Kroes TTC, mutagenicity, and carcinogenicity. As demonstrated in Table 4, the test compounds have been shown to be safe and do not possess any mutagenic or carcinogenic properties. (Wang et al., 2023)

Conclusion

Research has shown that gallic acid compounds can inhibit the activity of arabinosyltransferase c enzyme in silico and have the potential to be developed as an antituberculosis drug candidate.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

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