Unraveling the Therapeutic Potential of *Andrographis paniculata* for Tuberculosis: Molecular Docking Study

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Abstract

Tuberculosis (TB) remains a global health challenge with increasing drug resistance. This study aims to explore the potential of *Andrographis paniculata* as an alternative anti-TB therapy through an in silico approach. The study was conducted using the molecular docking method using Biovia Discovery Studio, AutoDock 1.5.7, and ChemDraw 3D software. The target proteins analyzed were 1TYP and 3R6C, which play a role in the biosynthesis of *Mycobacterium tuberculosis* cell walls. The docking results showed that dehydroandrographolide and neoandrographolide compounds have lower binding energies than ethambutol, with ΔG values of -9.54 kcal/mol and -9.04 kcal/mol at 3R6C, respectively. Stable hydrogen and non-hydrogen interactions indicate a stronger inhibitory potential against protein targets. Pharmacokinetic analysis through SwissADME and PKCMS confirmed that this compound meets Lipinski's Rule of 5 criteria and has lower toxicity compared to conventional TB drugs. Thus, this study provides new insights into the development of natural compound-based TB therapy, which is potentially more effective and has minimal side effects. Further studies are needed to confirm the activity of this compound through in vitro and in vivo tests.

Keywords: *Andrographis paniculata, molecular docking, tuberculosis,*

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Highlights

1. Dehydroandrographolide showed the strongest binding affinity to 3R6C protein with a ΔG of -9.54 kcal/mol, surpassing even the control drug ethambutol.
2. Neoandrographolide and andrographolide also demonstrated strong binding affinities and stable interactions with both 1TPY and 3R6C targets.
3. All tested compounds from *Andrographis paniculata* complied with Lipinski's Rule of Five and showed no AMES or hepatotoxicity based on ADMET predictions.
4. Compared to ethambutol, *A. paniculata* derivatives had stronger molecular docking interactions and lower predicted toxicity, including the absence of skin sensitization.
5. These findings suggest *A. paniculata* compounds have potential as safe, natural, and multitarget TB inhibitors, supporting further *in vitro* and *in vivo* validation.

Introduction

Tuberculosis (TB) remains one of the leading causes of mortality among infectious diseases globally. The World Health Organization (WHO) has set an ambitious target to reduce TB incidence by 90% by 2035 under its End TB Strategy (Tobin & Tristram, 2024). This disease is caused by the acid-fast bacterium *Mycobacterium tuberculosis*, discovered in 1883 by Robert Koch (Tobin & Tristram, 2024). Its unique lipid-rich cell wall contributes to intrinsic resistance against many antibiotics and host immune defenses, enabling prolonged survival within macrophages (Warner et al., 2015). In 2020 alone, approximately 167,000 deaths occurred from 7.5 million newly diagnosed TB cases worldwide (WHO, 2023). Comorbid conditions, particularly *Human Immunodeficiency Virus*/Acquired Immunodeficiency Syndrome (HIV/AIDS), have been shown to significantly elevate TB-related mortality (Hamada et al., 2021; Kwan & Ernst, 2011).

Clinically, TB is categorized into drug-sensitive TB and drug-resistant TB, with the latter posing a critical public health threat due to treatment failure and transmission risks (Alsayed & Gunosewoyo, 2023; Williams et al., 2023). Resistance arises from various mechanisms, including target modification, efflux pump overexpression, and enzymatic drug inactivation, which necessitate the exploration of new molecular entities and treatment strategies (Chiang et al., 2010; Migliori et al., 2020). Current research has identified several essential protein targets in *M. tuberculosis*, such as DNA gyrase, ATP synthase subunit c, and membrane transporter MmpL3, which are vital for bacterial replication, energy metabolism, and cell wall biosynthesis, respectively (Koul et al., 2007; Locher et al., 2015; Xu et al., 2017). The discovery of new TB drugs through phenotypic screening has shown efficacy against resistant *M. tuberculosis* (Manjunatha & Smith, 2015; Mdluli et al., 2015).However, many first-line anti-TB drugs are associated with significant side effects, including hepatotoxicity, gastrointestinal disturbances, and neurotoxicity, which can impact patient adherence and therapeutic outcomes (Sotgiu et al., 2015; Zumla et al., 2015).

Given these limitations, the search for novel, safer, and multitarget anti-TB agents has become increasingly urgent (Gautam et al., 2023). Natural products have emerged as a promising source of antimicrobial compounds due to their structural diversity and biological activities. One promising approach is the use of herbal products as alternative therapies, such as *Hibiscus cannabinus, Sesbania grandiflora,* and *Andrographis paniculata* (Bindhu et al., 2014; Das et al., 2013; Prabu et al., 2015). Among these, *A. paniculata*, a medicinal herb widely used in traditional systems of medicine, has attracted attention for its antimicrobial and immunomodulatory potential. This received attention in research due to its bioactive compounds, especially andrographolide, neoandroghapolide, 14-dioxyandrogapolide, and dehydroandroghapholide which has antibacterial and anti-inflammatory activities that have the potential to inhibit the growth of *M. tuberculosis.* (Okhuarobo et al., 2014; Singh et al., 2017). Previous studies have shown that this plant has great prospects as a therapeutic agent for TB, exhibit strong binding affinities toward key *M. tuberculosis* target proteins, including FtsZ (2Q1X), DprE1 (4FDO), and PanK (4BFS) (Haridas et al., 2017). These findings highlight the plant's potential as a source of anti-TB drug candidates and support its future use in tuberculosis treatment strategies.

Despite these promising findings, comprehensive computational studies focusing on the interaction of *A.*

paniculata constituents with validated TB targets remain limited. Therefore, this study aims to investigate the anti-TB potential of major bioactive compounds from *A. paniculata* using an in silico approach involving molecular docking and absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions. By identifying the most promising compound-target interactions, this research seeks to contribute to the development of safer, more effective, and multitarget TB therapies derived from natural sources.

Research Methods

Tools and materials

This study was conducted using an MSI Modern 14 laptop, which was equipped with an Intel Core i5-1235U processor (up to 4.50 GHz), 16GB of RAM, and 512GB of internal storage. The software employed in the research included Biovia Discovery Studio 2024 for molecular visualization and interaction analysis, Avogadro for ligand structure optimization, ChemDraw 3D 2019 for energy minimization, and AutoDock 1.5.7 for molecular docking simulations.

The primary protein structures were retrieved from the Protein Data Bank (PDB). Two protein targets were selected due to their key roles in the metabolism of Mycobacterium tuberculosis: MmaA2 (PDB ID: 1TPY), involved in cell wall biosynthesis, and TrpD (PDB ID: 3R6C), a critical enzyme in the tryptophan biosynthesis pathway. These proteins were considered potential targets for novel anti-tuberculosis agents. The test ligands andrographolide (CID: 5318517), neoandrographolide (CID: 9848024), 14-dioxyandrographolide (CID: 11624161), and dehydroandrographolide (CID: 78577438) were selected based on previous studies and were obtained from the PubChem database. Ethambutol (CID: 14052), a standard anti-tuberculosis drug with low resistance, was used as a positive control (Mase & Chorba, 2019; Prabu et al., 2015).

Protein and ligand preparation

Protein preparation was performed by removing native ligands, water molecules, and non-essential heteroatoms using Biovia Discovery Studio (Farid, Rastrani, et al., 2025). The 3D structures of the test ligands were optimized using Avogadro to generate the most stable conformations. Subsequently, energy minimization was carried out using ChemDraw 3D to refine the molecular geometries and ensure that the structures were in their lowest energy state prior to docking (Syahputra et al., 2022).

Docking validation and simulation

The docking protocol was validated through a redocking procedure, in which the native ligand was re-docked into the original active site of the protein. The accuracy of this process was evaluated using the Root Mean Square Deviation (RMSD) value, an RMSD of less than 2 Å indicated a reliable reproduction of the original binding pose (Ramírez & Caballero, 2018). The coordinates from the validated redocking were used to define the grid box for subsequent docking simulations.

Molecular docking was conducted using AutoDock 1.5.7, with the genetic algorithm selected as the search method. The test ligands were docked into the binding pockets of the prepared protein targets using grid parameters established during the validation step. The resulting binding affinities were analyzed based on the estimated binding free energy (ΔG), with more negative values indicating stronger interactions. The docking outcomes were visualized and analyzed using Biovia Discovery Studio, which allowed for the identification of key interactions such as hydrogen bonding and hydrophobic contacts between ligands and amino acid residues at the active site. (Lestariningrum et al., 2024).

Pharmacokinetic prediction

Pharmacokinetic and Toxicity Prediction To evaluate the drug-likeness and safety profile of the test compounds, in silico pharmacokinetic and toxicity predictions were conducted using SwissADME and pkCSM (Utami et al., 2025). The analysis included assessments of Lipinski's Rule of Five, along with predictions of hepatotoxicity and Ames mutagenicity (Farid, Al Madury, et al., 2025). These parameters provided a preliminary understanding of each compound's potential as a safe and effective therapeutic agent (Ramadhan et al., 2024).

Results and Discussion

The crystal structure of the protein, identified as PDB ID 3R6C, provides crucial information on the substrate recognition mechanism of anthranilate phosphoribosyltransferase (AnPRT) in *M. tuberculosis* (Castell et al., 2013). This indicates a strong interaction between the enzyme and its substrate, offering strategic insights for the rational design of inhibitory compounds (Castell et al., 2013). The visualization of the enzyme's active site reveals specific molecular interactions that could be targeted for drug development against tuberculosis. The 1TPY protein corresponds to the cyclopropane synthase MmaA2, which plays a significant role in synthesizing mycolic acids, essential components of the *M. tuberculosis* cell wall (Buannata et al., 2024). Determined through X-ray crystallography at 2.20 Å resolution, this structure offers a comprehensive view of the enzyme's catalytic site and its substrate-binding features (Buannata et al., 2024). To expand the investigation into potential inhibitors, computational docking was performed using two protein targets, 3R6C and 1TPY.

Table 1. Results of Docking Method Using Redocking

Natural Ligands	Number of Grids			Grid Coordinates			Grid Spacing	RMSD
1TPY	**X**	**Y**	**Z**	**X**	**Y**	**Z**	0.375 A	0.828 A
	40	40	40	42.255	26,795	44,407		
3R6C	**X**	**Y**	**Z**	**X**	**Y**	**Z**	0.375 A	1.813 A
	40	40	40	1.174	4.159	30.124		

The results of the validation method using redocking showed that both proteins, 1TYP and 3R6C, had good validity with RMSD of less than 2 Å each, as seen in Table 1 (Ramírez & Caballero, 2018). Redocking on the 1TYP protein resulted in a low RMSD of 0.828 A, indicating that there was no significant change in the position of the native ligand before and after redocking, as seen in Figure 1. The grid box on 1TYP with ligand coordinates X: 42.255, Y: 26.795, Z: 44.407 provided a stable and reliable docking position. Meanwhile, redocking on 3R6C yielded an RMSD of 1.813 A, which also indicated good validity, as shown in Figure 1. The grid box on 3R6C with ligand coordinates X: 1.174, Y: 4.159, Z: 30.124 provided a more stable docking position, indicating the reliability of this redocking method for further analysis.

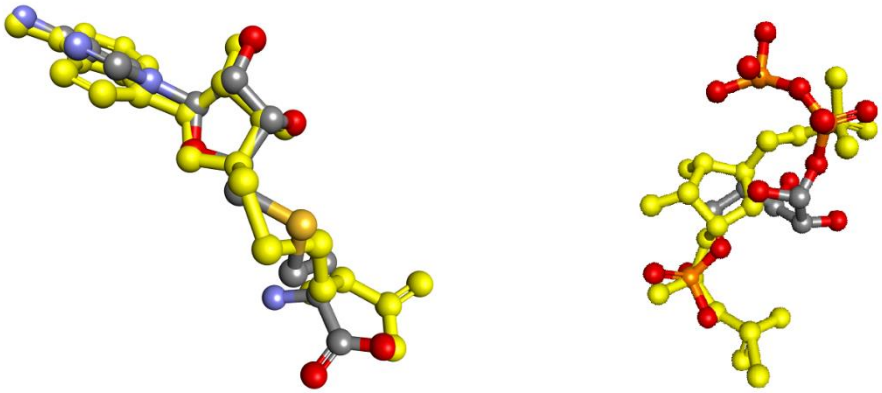

Figure 1 Overlap of Natural Ligand (Gray) and Post-Redocking Ligand (Yellow)

Based on the results of the docking analysis in Table 2, the affinity of the ligands to the target protein PDB 1TPY shows good affinity. The native ligand has the best affinity with a binding energy of--10.33, followed by andrographolide with a binding energy -9.48. Furthermore, 14-dioxyandrographolide has a binding energy of -9.47, having a binding value that is slightly different from andrographolide, then dehydroandrographolide follows with a binding energy of -9.40. Neoandrographolide is in fourth place with a binding energy of -8.58. Finally, ethambutol shows the weakest affinity with a binding energy of -5.63, indicating that its interaction with the active site is weaker compared to other ligands.

The native ligand exhibited the strongest binding affinity with a binding energy of -10.33 kcal/mol. It forms multiple hydrogen bonds with residues such as Tyr33, Trp75, Gly72, and Gln99, which significantly enhance the stability of the ligand–enzyme complex. Additionally, non-hydrogen interactions, including Pi-Alkyl and Pi-Sigma bonds with residues Leu95, Ala123, and Tyr16, further strengthen the ligand's association with the active site, contributing to its high inhibitory efficiency (Figure 2). In contrast, andrographolide showed a slightly lower binding affinity. Its interactions primarily involve hydrogen bonds with hydrophobic and polar residues such as Tyr16, Tyr232, Cys73, and Thr78. However, andrographolide lacks substantial non-hydrogen interactions, suggesting that its binding may be less stable compared to other ligands that form stronger hydrophobic contacts (Grangeasse et al., 2010). This is reflected in its comparatively reduced inhibitory potential. 14-dioxyandrographolide forms hydrogen bonds with Tyr16, Thr78, and Cys72, but also exhibits less favorable non-hydrogen interactions, such as with Gly127, indicating suboptimal binding. Despite this, its relatively high binding energy -9.47 indicates potential inhibitory activity, albeit less efficient than the native ligand. Meanwhile, the control drug ethambutol showed multiple interactions with residues including Thr78, Gly72, and Gln99, but demonstrated a higher is less favorable binding energy -5.63. Although ethambutol forms hydrogen bonds with Tyr12 and Tyr16, the absence of significant non-hydrogen bonding contributes to its lower affinity for the active site and correlates with its limited inhibitory efficacy (Dyas et al., 2023).

Table 2. Docking Simulation Results on 1TYP

Test Ligand	Binding Energy (ΔG) kcal/mol	Hydrogen Bonds	Non-Hydrogen Bonds
Native ligand	-10.33	Tyr33, Trp75, Gly72, Gly74, Gln99, Thr94, Val12, Thr 94, Ala121, Leu95, Gly122, Trp123, Glu124	Leu95, Ala123 (Pi-Alkyl), Leu95, Tyr16 (Pi-Sigma), Gly137, His141 (Pi-Sulfur)
Andrographolide	-9.48	Tyr16, Tyr232, Cys73, Thr78, Thr78	-
Neoandroghapolide	-8.58	Trp123, Glu124, Gly122, Gly72, Tyr33, Thr78	His141, Ala139, Tyr16, Tyr16 (Pi-Alkyl), Tyr16 (Pi-Sigma)
14 dioxyandrogapolide	-9.47	Tyr16, Thr78, Thr78, Cys72	Gly127 (Unfavorable Acceptor)
Dehydroandroghapholide	-9.40	Gly72, Gls31, Tyr33, Ser34	-
Ethambutol	-5.63	Thr78, Asp70, Asp70, Gly72, Gly72, Gly72, Gln99, Ile136, Ile136	Tyr12, Tyr16 (Pi-Alkyl)

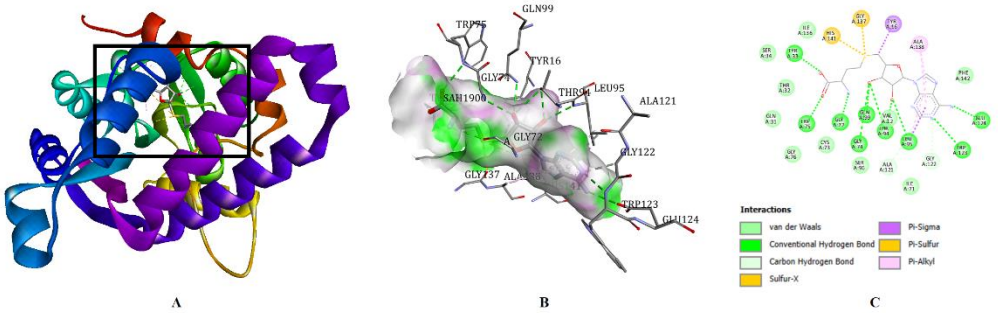

Figure 2 Native ligand interaction with 1TYP protein. (A) protein structure, (B) interaction pocket, (C) amino acid interaction.

Based on the binding energy (ΔG) analysis in Table 3, the test compounds, such as dehydroandrographolide and neoandrographolide, showed greater potential to inhibit 3R6C protein compared to native ligands and Ethambutol as a control. With ΔG of -9.54 kcal/mol and -9.04 kcal/mol, respectively, these two compounds have lower binding energies, indicating a more stable and stronger interaction with the active site of the 3R6C protein. In contrast, the native ligand and Ethambutol showed higher binding energies, namely -7.37 and -6.91,

indicating that the test compounds have lower affinity and weaker inhibitory potential. Thus, dehydroandrographolide and neoandrographolide have greater potential to inhibit 3R6C protein, making them more promising candidates in the development of antibacterial therapy compared to standard controls such as Ethambutol

Table 3. Docking Simulation Results on 3R6C

Test Ligand	Binding Energy (ΔG) kcal/mol	Hydrogen Bonds	Non-Hydrogen Bonds
Native Ligand	-7.37	Gly137, Gly146, Ser119, Ser145, Gly147, Ser143, Ser143, Ser143, Gly110, Ala141, Ser142, Arg193, Gly107	Arg193, Arg193, Lys135, Lys135 (Salt Bridge), Asp11, Asp251 (Unfavorable Negative)
Andrographolide	-8.39	Glu252, Glu252, Ser119, Ser119, Ser119, Arg193, Gly110	Gly110 (Unfavorable Donor)
Neoandroghapolide	-9.04	Asn138, Thr120, Leu118, Glu252, Thr115, Val116	Ser119 (Unfavorable Donor), Ala141, Ala141 (Pi-Alkyl)
14 Dioxyandrogapolide	-7.91	Asn138, Gly147, Thr115, Va116, Asp111, Ser143	-
Dehydroandroghapholide	-9.54	Thr115, Thr115, Val116, Leu118, Ser142, Ser143, Thr108	-
Ethambutol	-6.91	Glu252, Glu252, Asp251, Asp251, Aps111, Aps111, Ser143, Thr115	Ser119 (Unfavorable Donor)

Dehydroandrographolide exhibited the highest binding affinity toward the 3R6C protein, with a binding energy of ΔG -9.54. This strong affinity is supported by the formation of multiple hydrogen bonds with key residues including Thr115, Val116, Leu118, Ser142, Ser143, and Thr108, which are located within or near the enzyme's catalytic site Figure 3. These interactions contribute significantly to the stability of the ligand–protein complex and suggest its potential as a strong enzyme inhibitor. Neoandrographolide also demonstrated favorable binding, with a binding energy of ΔG -9.04. It forms hydrogen bonds with residues such as Asn138, Thr120, Leu118, Glu252, and Thr115. Although it exhibits a less favorable non-hydrogen interaction with Ser119, the overall binding configuration remains stable and supports its inhibitory potential. In contrast, the control drug Ethambutol displayed a lower binding affinity with a

ΔG of -6.91. While it interacts via hydrogen bonding with Glu252, Asp251, and Ser143, the presence of non-optimal non-hydrogen interactions, particularly involving Ser119 as an unfavorable donor, diminishes its affinity and inhibitory efficacy (Venugopala et al., 2021). The native ligand, as reported by Ma et al. (2018), forms hydrogen bonds with Gly137, Gly146, and Ser119, along with non-hydrogen interactions with Arg193 and Lys135, including salt bridge interactions. These contribute to the stability of the ligand–protein complex, although some unfavorable non-hydrogen contacts reduce its overall affinity when compared to the more stable interactions observed with dehydroandrographolide and neoandrographolide (Ma et al. 2018.

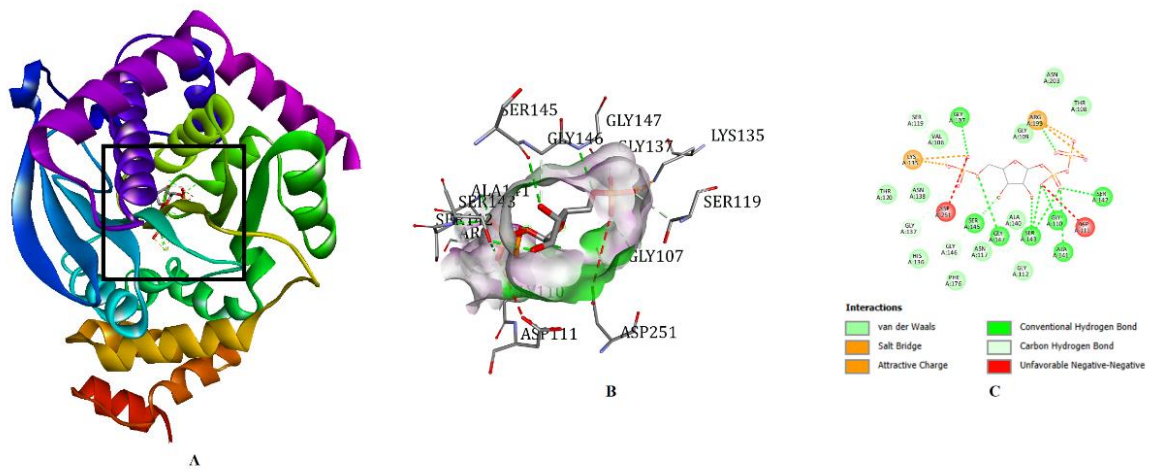

Figure 3 Native ligand interaction with 3R6C protein. (A) protein structure, (B) interaction pocket, (C) amino acid interaction.

The interaction of ligands with specific amino acid residues in the target proteins (1TPY and 3R6C) plays a critical role in determining their inhibitory potential. These residues are often located within or near the enzyme's active site and are directly involved in catalysis or substrate binding. When a ligand forms hydrogen bonds and hydrophobic contacts with these key residues, it can stabilize the protein-ligand complex, thereby increasing binding affinity and potentially inhibiting enzymatic activity (Ma et al. 2018). The 3R6C protein, involved in vital metabolic functions of *M. tuberculosis*, and 1TPY, related to regulatory pathways, are essential for bacterial survival. Ligands that interact effectively with catalytic or regulatory residues in these proteins may disrupt their biological function, leading to inhibited bacterial growth (Dyas et al., 2023). Therefore, the strength and specificity of these amino acid interactions can directly influence the efficacy of the compounds as potential antituberculosis agents (Dyas et al., 2023).

The findings of this study align well with prior research that has consistently highlighted the therapeutic potential of *A. paniculata* in tuberculosis management. Bhatter et al., (2015) demonstrated the plant's inhibitory effect on *M. tuberculosis* growth under hypoxic conditions, emphasizing its possible role against dormant bacilli. Similarly, clinical evidence from (Widhawati et al., 2015) confirmed that supplementation with *A. paniculata* significantly accelerated sputum conversion and improved clinical outcomes when used alongside standard anti-TB therapy. Moreover, Prabu et al., (2015) identified andrographolide a major bioactive compound in *A. paniculata* as an antimycobacterial agent with predicted

molecular targets validated through docking simulations, supporting its mechanism-based action. Complementing these findings, Sharma et al., (2022) further established the extract's protective role against drug-induced nephrotoxicity, adding another dimension to its utility in TB treatment regimens. Collectively, these results reinforce the consistency of in silico predictions with existing experimental and clinical data, thereby strengthening the rationale for advancing *A. paniculata* as a promising adjunct or lead candidate in tuberculosis drug development.

Table 4. ADMET prediction results

Test Ligand	Andro-grapholide	Neo-androghapolide	14 Dioxy-androgapolide	Dehydro-androghapholide	Ethambutol
Molecular weight	350.45 g/mol	480.59 g/mo	334.45 g/mol	332.43 g/mol	204.31 g/mol
H-Bond Acceptor	5	7	4	4	4
H-Bond Donor	3	8	4	2	4
Log P	1.98	1.26	2.81	2.72	0.18
TPSA	86.99 Å	125.68 Å	66.76 Å	66.76 Å	64.52 Å
AMES toxicity	No	No	No	No	No
Hepatotoxicity	No	No	No	No	No
Skin Sensitization	No	No	No	No	Yes

Pharmacokinetics prediction of the five test compounds, namely andrographolide, neoandrographolide, 14-deoxyandrographolide, dehydroandrographolide, and ethambutol as TB control drugs, showed significant variations in pharmacokinetic and toxicological parameters, as seen in Table 4. Ethambutol, which is used as a control drug for TB, has the lowest molecular weight of 204.31 g/mol, which generally supports better membrane permeability. Other compounds, such as neoandrographolide and andrographolide, have higher molecular weights, which may reduce oral absorption. The Log P of ethambutol is 0.18, indicating higher hydrophilicity compared to other compounds, which have Log P between 1.26 and 2.81, indicating a higher possibility of tissue distribution for other compounds. The Topological Polar Surface Area (TPSA) value of ethambutol, 64.52 Å, is relatively smaller compared to neoandrographolide, 125.68 Å, which indicates the possibility of better membrane permeability for ethambutol compared to other compounds having higher TPSA (Abdurrahman et al., 2021).

In terms of toxicity, all tested compounds did not show any potential toxicity based on AMES toxicity and hepatotoxicity parameters, indicating that these compounds have a low probability of causing mutagenicity and liver damage (Ramadhan et al., 2024). However, ethambutol showed a possibility of causing skin sensitivity, which was not seen in other compounds (Syahputra et al., 2022). From an ADMET perspective, 14-deoxyandrographolide and dehydroandrographolide had higher Log P values of ~2.8, indicating a better distribution in fat tissue compared to ethambutol. However, all compounds showed a relatively high number of donor and acceptor H-bonds, which may affect solubility and interaction with biological targets. Based on this analysis, although compounds from andrographolide derivatives have promising pharmacokinetic characteristics, further

evaluation through in vivo and clinical studies is needed to determine their effectiveness as alternative candidates in TB therapy.

Conclusions

This study identified dehydroandrographolide as the most promising antituberculosis candidate based on its strong binding affinity to the 3R6C protein -9.54 kcal/mol and favorable interactions with key catalytic residues. Neoandrographolide also showed potent inhibition of both 1TPY and 3R6C proteins. All test compounds demonstrated acceptable ADMET profiles with no predicted toxicity, except for ethambutol, which showed potential skin sensitization. These findings support the potential of *Andrographis paniculata* derivatives as effective inhibitors of *M. tuberculosis* enzymes and warrant further investigation through in vivo and clinical validation.

Author Contributions

MF was responsible for the conceptualization and overall supervision of the research. ASM contributed to the development of the methodology and assisted in data collection. ZQA carried out data analysis and contributed to the preparation of data visualizations. SAM took part in writing the initial draft and was involved in the review and editing process. MF and SAM also handled project administration and secured funding for the study. All authors contributed to the refinement of the manuscript and approved the final version.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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