Journal of Science and Technology, Vol. 44, No. 1 (2026), pp. 38 - 46
Kwame Nkrumah University of Science and Technology (KNUST)
https://dx.doi.org/10.4314/just.v44i1.3

IN SILICO EVALUATION OF PHYTOCHEMICALS FROM ICACINA TRICHANTHA AS POTENTIAL ANTI-TUBERCULOSIS AGENTS

Taye Alawode*
Department of Chemistry, Federal University Otuoke, Nigeria
***Corresponding author: onatop2003@yahoo.com**

ABSTRACT
The emergence of drug-resistant strains of Mycobacterium tuberculosis and the limitations of current therapies has necessitated a search for more effective drugs for tuberculosis. This study investigates phytoconstituents from the Icacina trichantha tubers as potential anti-tuberculosis agents. A molecular docking approach, employing SwissDock, was used to evaluate the interactions of twenty (20) phytoconstituents with key M. tuberculosis proteins, including DprE1 (6HEZ), InhA (1ENY), KasA (2WGE), PanK type 1 (4BFT), PknB (2FUM), and Pks13 (5V3X). Furthermore, the compounds were screened for drug-likeness and toxicity using SwissADME and admetSAR, respectively. The results revealed that most phytochemicals exhibited superior binding affinities compared to standard anti-tuberculosis drugs. Icaceine, humirantholide C, icacinlactone G, 17-hydroxyicacinol, and hydroxyicacinlactone B were identified as the most promising candidates based on their binding energies. Drug-likeness evaluations confirmed that all the compounds met Lipinski's criteria. Toxicological analysis (using admetSAR) revealed that the compounds were non-carcinogenic, non-AMES toxic, and weak HERG channel inhibitors, however, in vitro and in vivo assessments are needed to validate these findings. This study highlights the potential of phytochemicals in tubers of Icacina trichantha as promising leads for anti-tuberculosis drug development.

Keywords: Tuberculosis, *Icacina trichantha*, molecular docking, drug-likeness.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health burden. In 2023, an estimated 10.8 million people were infected with TB worldwide; 1.25 million people died from the disease within the same year, restoring it as the leading cause of death from a single infectious agent worldwide. Also, it was the leading killer of people with HIV and a major cause of deaths related to antimicrobial resistance (WHO, 2024). The disease's incidence is disproportionately higher in low – and middle-income countries. For example, in 2022 most TB cases were in the WHO regions of South-East Asia (46%), Africa (23%) and the Western Pacific (18%), with smaller shares in the Eastern Mediterranean (8.1%), the Americas (3.1%) and Europe (2.2%) (WHO, 2023). Current tuberculosis treatment regimens are prolonged and complex, often requiring a combination of antibiotics administered over six months or more. Challenges such as drug resistance, adverse side effects, and patient non-compliance exacerbate treatment difficulties (Tuyiringire *et al*., 2022). The emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) further complicates therapeutic strategies, necessitating the exploration of novel anti-tubercular agents (Sharma and Yadav, 2016).

In silico techniques, particularly molecular docking studies, have revolutionized drug discovery by enabling the virtual screening of compounds against specific biological targets. These computational methods offer advantages such as cost-effectiveness, time efficiency, and the ability to predict binding affinities and interactions at the molecular level (Pinzi and Rastelli, 2019). In this study, the antimycobacterial potential of twenty (20) compounds (Figure 1)

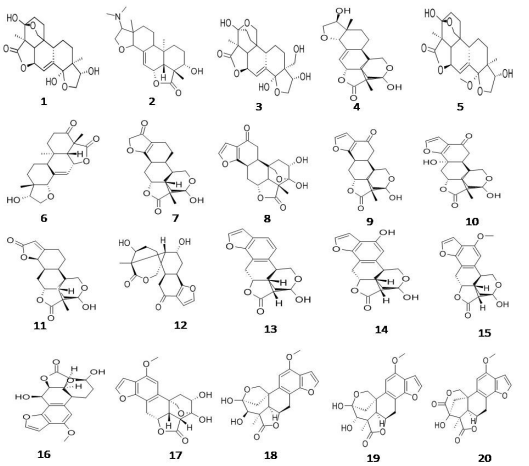

Figure 1: *Icacina trichantha* compounds: Icacinol (1), Icaceine (2), 17-hydroxyicacinol (3), Humirianthol (4), Methoxyhumirianthol (5), Icacinlactone I (6), Humirantholide C (7), Icacenone (8), Icacinlactone E (9), Icacinlactone F (10), Icacinlactone G (11), Icacinlactone J (12), Icacinlactone A (13), Hydroxyicacinlactone A (14), Icacinlactone B (15), Hydroxyicacinlactone B (16), Icacinlactone H (17), Icacinlactone C (18), Icacinlactone D (19), Icacintrichantholide (20)

The antimicrobial properties of extracts of *Icacina trichantha* have been previously reported (Otun *et al*., 2015). In the ethnomedicinal practices of southwestern

Nigeria, the leaves and seeds of the plant have been used to treat hypertension and asthma (Ajibesin *et al*., 2008); the tubers and leaves are used as aphrodisiacs (Quattrocchi, 2012). The plant is also used as first-aid treatment for food poisoning (Mbatchou and Dawda, 2012). Additionally, the tubers of the plant are allegedly effective in the treatment of tuberculosis. A previous study reported the isolation of an antimycobacterial compound from the chloroform extract of the tuber of the plant (Akoh *et al*., 2024). This study systematically evaluates compounds isolated from *Icacina trichantha* for anti-tubercular activity using in silico methodologies (Che *et al*., 2016). By integrating computational techniques with phytochemical research, this study seeks to identify promising lead candidates for further development, potentially contributing to the diversification and enhancement of TB treatment options.

MATERIALS AND METHODS

Selection of Compounds

Twenty (20) bioactive compounds previously isolated from tubers of *Icacina trichantha* (Che *et al*., 2016), along with five (5) standard drugs used for treating tuberculosis (ethambutol, Isoniazid, Pyrazinamide, ciprofloxacin, and clofazimine) were selected for this study. The standard drugs served as control against which the activities of the phytochemicals were measured.

Selection of Target Proteins

The 3D structures of six proteins associated with the pathogenesis and survival of *Mycobacterium tuberculosis* were retrieved from the Protein Data Bank in the PDB format (www.rcsb.org). These include: DprE1 (6HEZ), InhA (1ENY), KasA (2WGE), PanK type 1 (4BFT), PknB (2FUM), and Pks13 (5V3X). Previous studies have highlighted the suitability of these proteins for anti-tubercular drug development (Baptista et al., 2021).

Molecular Docking

Molecular docking studies were performed using SwissDock. The ligands and the proteins were uploaded via spaces provided on the webserver and docking was carried out using the AutoDock Vina option (Bugnon et al., 2024; Eberhardt et al., 2021). The docking results were analyzed to identify the binding poses with the least binding energy, as these are indicative of stronger interactions.

Drug-Likeness and Toxicity Assessment

The potential drug-likeness of the compounds was assessed using the Lipinski's Rule of Five. The physicochemical properties of the compounds were evaluated using SwissADME (Daina *et al*., 2017). The parameters evaluated included molecular weight, topological polar surface area (TPSA), number of hydrogen bond acceptors/donors, number of rotatable bonds, ability of the compound to cross the blood-brain barrier, among others. Toxicological profiles were predicted using AdmetSAR (Cheng *et al*., 2012), an in silico tool for predicting human and environmental toxicity.

RESULTS AND DISCUSSION

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide. The ability of the causative agent, *Mycobacterium tuberculosis*, to evade the host immune system and develop resistance to conventional therapies necessitates the identification of novel therapeutic agents (Chandra *et al*., 2022). This study evaluated the potential of phytoconstituents isolated from *Icacina trichantha* tubers as anti-tuberculosis agents by targeting key proteins essential for the pathogenesis and survival of M. tuberculosis. DprE1, a decaprenylphosphoryl-d-ribose oxidase, is involved in the biosynthesis of decaprenylphosphoryl-D-arabinose, an essential component of the mycobacterial cell

wall (Crellin *et al* , 2011; Wolucka, 2008). InhA, KasA and Pks13 are essential for the synthesis of mycolic acid by M. tuberculosis (Schaeffer *et al*., 2001; Portevin *et al* , 2004). Mycolic acid forms the waxy cell envelope essential for the bacterium's virulence and drug resistance (Nataraj *et al*., 2015). Pantothenate kinase (PanK) participates in coenzyme A biosynthesis, which is crucial for fatty acid metabolism and energy production (Das *et al*., 2006). PknB, a serine/threonine-protein kinase, determines cell shape, morphology and possibly cell division (Chawla *et al*., 2014). Binding of compounds to these proteins can inhibit their activity, thereby impairing bacterial survival and replication.

The molecular docking results revealed that most of the compounds exhibited better binding affinities to the selected target proteins than the standard anti-tubercular drugs (including ethambutol, isoniazid, pyrazinamide, ciprofloxacin, and clofazimine), implying that they may exhibit stronger inhibitory effects on the target proteins, potentially leading to enhanced therapeutic efficacy. Table 1 presents the binding affinities of the compounds against the target proteins.

Table 1: Binding affinities of compounds against target protei

Compound	6HEZ (kcal/mol)	1ENY (kcal/mol)	2WGE (kcal/mol)	4BFT (kcal/mol)	2FUM (kcal/mol)	5V3X (kcal/mol)
1	-8.384	-6.839	0.883	-10.509	-6.809	-4.545
2	-8.712	-6.980		-10.302	-6.474	-2.919
3	-7.823	-5.737		-10.661	-5.672	-3.702
4	-8.522	-4.652	-1.708	-10.568	-5.913	-4.619
5	-8.214	-5.850	0.806	-10.047	-6.054	-4.671
6	-8.564	-6.557	-3.262	-9.968	-6.286	-5.276
7	-8.199	-8.408	-5.044	-10.200	-6.701	-5.086
8	-8.039	-	-4.249	-10.299	-6.479	-5.193
9	-8.329	-7.140	-4.275	-10.266	-6.653	-4.935
10	-8.318	-8.115	-5.010	-10.452	-6.159	-4.955
11	-8.368	-7.501	-5.187	-10.335	-7.068	-4.626
12	-8.052	-7.744	-2.421	-9.899	-6.014	-4.967
13	-7.706	-7.079	-4.852	-9.285	-6.936	-5.862
14	-7.739	-7.157	-4.216	-9.693	-6.857	-5.562
15	-7.595	-6.802	-1.227	-9.591	-6.952	-5.646
16	-7.182	-7.360	1.081	-9.563		-5.914
17	-7.460	-3.795	-2.921	-9.651	-6.820	-5.627
18	-7.720	-6.259	2.036	-9.904	-6.554	-5.594
19	-7.815	-5.983	0.818	-9.834	-6.458	-5.537
20	-7.964	-7.889		-9.837	-6.350	-5.691
ethambutol	-3.864	-4.490	-3.885	-5.223	-3.526	-4.374
Isoniazid	-4.409	-5.064	-3.944	-5.124	-3.956	-4.461

Pyrazinamide	-3.741	-4.427	-3.957	-4.755	-3.463	-4.058
ciprofloxacin	-6.509	-6.502	-3.117	-8.828	-6.059	-5.630
clofazimine	-8.005	-	10.765	-10.252	-7.607	-6.419

From Table 1, it can be seen that Icaceine (with a binding energy of – 8.712 kcal/mol) had the highest binding affinity against DprE1 (6HEZ); Humirantholide C (with a binding energy of – 8.408 kcal/mol) showed the best affinity against InhA (1ENY); Icacinlactone G (with a binding energy of – 5.187 kcal/mol) was the most active compound against KasA (2WGE); 17-Hydroxyicacinol (with a binding energy of – 10.661 kcal/mol) exhibited the strongest affinity against PanK type 1(4BFT); Icacinlactone G (with a binding affinity of – 7.068 kcal/mol) also had the highest affinity against PknB (2FUM); while Hydroxyicacinlactone B (with a binding energy of – 5.914 kcal/mol) had the best binding affinity against Pks13 (5V3X). The binding poses of these ligands within the protein active sites are illustrated in Figure 2.

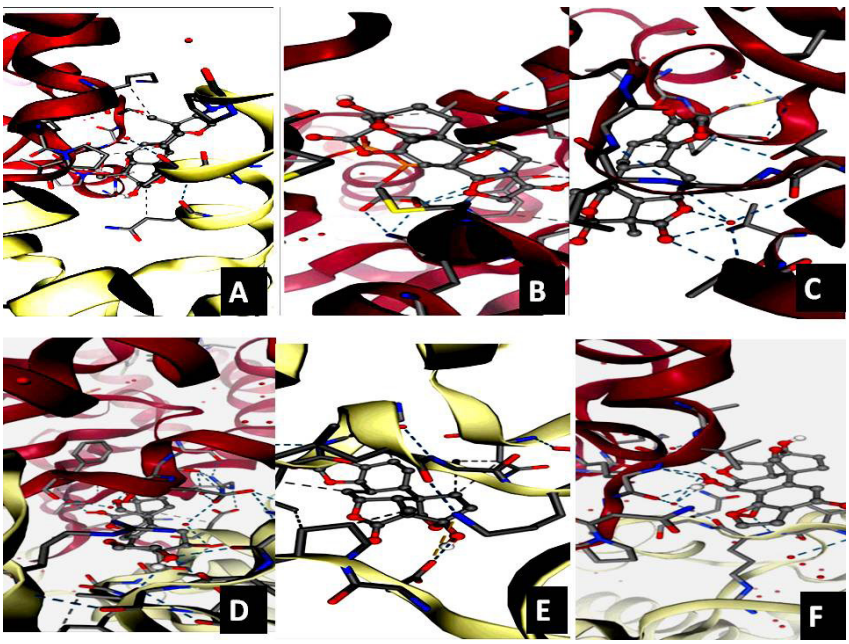

Figure 2: Binding poses of key compounds in the active sites of target proteins.

All the compounds investigated satisfied Lipinski's Rule of Five, which is a widely accepted guideline for predicting the drug-likeness of compounds (Table 2). According to this rule, a potential drug candidate should have molecular weight ≤ 500, ≤ 5 hydrogen bond donors, ≤ 10 hydrogen bond acceptors, and a logP ≤ 5 (Lipinski *et al*., 2001). Compounds that meet these criteria are more likely to have favorable pharmacokinetic properties, enhancing their potential as drug candidates.

Table 2: Drug-likeness and pharmacokinetic profiles of compounds

	MW	NRB	HBA	HBD	TSPA	iLogP	GI	BBB	P-gp	Lipinski
1	378.42	0	7	3	105.45	2.16	High	No	Yes	Yes
2	375.50	1	5	1	59.00	3.03	High	Yes	Yes	Yes
3	394.42	1	8	4	125.68	0.98	High	No	Yes	Yes
4	362.42	0	6	2	85.22	1.94	High	No	Yes	Yes
5	392.44	1	7	2	94.45	1.62	High	No	Yes	Yes
6	346.42	0	5	1	72.83	2.23	High	Yes	Yes	Yes
7	346.37	0	6	1	82.06	2.11	HIgh	No	Yes	Yes
8	360.36	0	7	2	106.20	1.60	High	No	Yes	Yes
9	344.36	0	6	1	85.97	1.85	High	No	Yes	Yes
10	360.36	0	7	2	106.20	1.43	High	No	Yes	Yes
11	346.37	0	6	1	82.06	1.60	HIgh	No	Yes	Yes
12	346.37	0	6	2	96.97	1.76	High	No	Yes	Yes
13	312.32	0	5	1	68.90	1.82	High	Yes	No	Yes
14	328.32	0	6	2	89.13	1.97	High	No	No	Yes
15	342.34	1	6	1	78.13	2.52	High	No	No	Yes
16	358.34	1	7	2	98.36	2.23	High	No	No	Yes
17	358.34	1	7	2	98.36	2.01	High	No	No	Yes
18	372.37	1	7	2	98.36	1.89	High	No	No	Yes
19	372.37	1	7	2	98.36	2.39	High	No	No	Yes
20	370.35	1	7	1	95.20	2.25	High	No	No	Yes

The ability of some compounds to cross the blood-brain barrier (BBB) suggests potential for treating tuberculosis infections in the central nervous system, including tuberculous meningitis, which is difficult to manage due to limited drug penetration (Madadi and Sohn, 2024). However, compounds identified as P-glycoprotein (P-gp) substrates may face challenges in maintaining therapeutic concentrations, as P-gp-mediated efflux could reduce drug accumulation in target tissues (Geldenhuys *et al*., 2015). Strategies such as co-administration with P-gp inhibitors may enhance the efficacy of these compounds (Nguyen *et al*., 2021).

Toxicological predictions using admetSAR suggested that the compounds have low carcinogenic and AMES toxicity potential. However, as these predictions are based on computational models, further in vitro and in vivo assessments are necessary to confirm these findings.

Table 3: Predicted toxicological properties of studied compounds based on AdmetSAR analysis

Compounds	HERG	AMES Toxicity	Carcinogenicity
1	Weak Inhibitor	No	No
2	Weak Inhibitor	No	No
3	Weak Inhibitor	No	No
4	Weak Inhibitor	No	No
5	Weak Inhibitor	No	No
6	Weak Inhibitor	No	No
7	Weak Inhibitor	No	No
8	Weak Inhibitor	No	No
9	Weak Inhibitor	No	No
10	Weak Inhibitor	No	No
11	Weak Inhibitor	No	No
12	Weak Inhibitor	No	No
13	Weak Inhibitor	No	No
14	Weak Inhibitor	No	No
15	Weak Inhibitor	No	No
16	Weak Inhibitor	No	No
17	Weak Inhibitor	No	No
18	Weak Inhibitor	No	No

CONCLUSION

This study highlights the potential of *Icacina trichantha* phytochemicals as anti-tubercular agents, leveraging molecular docking to provide insights into their mechanisms of action. The results showed that many of these compounds exhibited better binding affinities compared to standard anti-tuberculosis drugs, suggesting their potential as effective inhibitors of critical bacterial proteins. Furthermore, the compounds are drug-like and toxicological evaluations revealed promising safety profiles. However, the findings of this study are preliminary and serve as a foundation for guiding further bioassays and toxicity evaluations.

Conflict of Interest

The author declares that there are no conflicts of interest.

REFERENCES

Ajibesin, K.K., Ekpo, B.A., Bala, D.N., Essien, E.E., and Adesanya, S.A. (2008). Ethnobotanical survey of Akwa Ibom State of Nigeria. Journal of Ethnopharmacology, 115: 387–408.

Akoh, O.U., Anyanwu, B.C., and Mac-kalunta, O.M. (2024). Isolation, characterization, and antimycobacterial potency of a furan derivative from the chloroform crude extract of *Icacina trichantha* oliv tuber. Communications in Physical Sciences, 11(1): 39–46.

Baptista, R., Bhowmick, S., Shen, J., and Mur, L.A.J. (2024). Molecular docking suggests the targets of various molecules. SwissDock. Nucleic Acids Research, 52(W1): W324–W332. DOI: 10.1093/nar/gkae300.

Bugnon, M., Röhrig, U.F., Goullieux, M., Perez, M.A.S., Daina, A., Michielin, O., and Zoete, V. (2024). SwissDock 2024: major enhancements for small-molecule docking with Attracting Cavities and AutoDock Vina. Nucleic Acids Research, 52(W1): W324–W332. DOI: 10.1093/nar/gkae300.

Chandra, P., Grigsby, S.J., and Philips, J.A. (2022). Immune evasion and provocation by *Mycobacterium tuberculosis*. Nature Reviews Microbiology, 20(12): 750–766. doi: 10.1038/s41579-022-00763-4.

Chawla, Y., Upadhyay, S., Khan, S., Nagarajan, S.N., Forti, F., and Nandicoori, V.K. (2014). Protein kinase B (PknB) of *Mycobacterium tuberculosis* is essential for growth of the pathogen in vitro as well as for survival within the host. Journal of Biological Chemistry. 16;289(20):13858-75. doi: 10.1074/jbc.M114.563536.

Che, C.T., Zhao, M., Guo, B., and Onakpa, M.M. (2016). *Icacina trichantha*: A tropical medicinal plant. Natural Product Communications, 11(7): 1039–1042.

Cheng, F., Li, W., Zhou, Y., et al. (2012). admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. Journal of Chemical Information and Modeling, 52(11): 3099–3105.

Crellin, P.K., Brammananth, R., and Coppel, R.L. (2011). Decaprenylphosphoryl-β-D-Ribose 20 – epimerase, the target of benzothiazinones and dinitrobenzamides, is an essential enzyme in Mycobacterium smegmatis. PLoS ONE.

Daina, A., Michielin, O., and Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules. Scientific Reports, 7: 42717. https://doi.org/10.1038/srep42717.

Das, S., Kumar, P., Bhor, V., Surolia, A., and Vijayan, M. (2006). Invariance and variability in bacterial PanK: A study based on the crystal structure of *Mycobacterium tuberculosis* PanK. Acta Crystallographica Section D Biological Crystallography. 62(Pt 6):628-38. doi: 10.1107/S0907444906012728.

Eberhardt, J., Santos-Martins, D., Tillack, A.F., and Forli, S. (2021). AutoDock Vina 1.2.0: New docking methods, expanded force field, and Python bindings. Journal of Chemical Information and Modeling, 61(8): 3891–3898. DOI: 10.1021/acs.jcim.1c00203.

Geldenhuys, W.J., Mohammad, A.S., Adkins, C.E., and Lockman, P.R. (2015). Molecular determinants of blood–brain barrier permeation. Therapeutic Delivery. https://doi.org/10.4155/tde.15.32

Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 46(1-3): 3–26. doi: 10.1016/s0169-409x(00)00129-0.

Madadi, A.K., and Sohn, M.J. (2024). Comprehensive therapeutic approaches to tuberculous meningitis: Pharmacokinetics, combined dosing, and advanced intrathecal therapies. Pharmaceutics, 16(4): 540. doi: 10.3390/pharmaceutics16040540.

Mbatchou, V.C., and Dawda, S. (2012). Phytochemical and pharmacological profile of genus Icacina. Phytopharmacology, 2: 135–143.

Nataraj, V., Varela, C., Javid, A., Singh, A., Besra, G.S., and Bhatt, A. (2015). Mycolic acids: Deciphering and targeting the Achilles' heel of the tubercle bacillus. Molecular Microbiology, 98(1): 7–16. doi: 10.1111/mmi.13101.

Nguyen, T.T., Duong, V.A., and Maeng, H.J. (2021). Pharmaceutical formulations with P-glycoprotein inhibitory effect as promising approaches for enhancing oral drug absorption and bioavailability. Pharmaceutics, 13(7): 1103. doi: 10.3390/pharmaceutics13071103.

Otun, K.O., Onikosi, D.B., Ajiboye, A.T., and Jimoh, A.A. (2015). Chemical composition, antioxidant and antimicrobial potentials of *Icacina trichantha* Oliv. leaf extracts. Research Journal of Phytochemistry, 9(4): 161–174. https://doi.org/10.3923/rjphyto.2015.161.174.

Pinzi, L., and Rastelli, G. (2019). Molecular docking: Shifting paradigms in drug discovery. International Journal of Molecular Sciences, 20(18): 4331. doi: 10.3390/ijms20184331.

Portevin, D., de Sousa-D'Auria, C., Houssin, C., Grimaldi, C., Chami, M., and Guilhot, C. (2004). A polyketide synthase catalyzes the last condensation step of mycolic acid biosynthesis in mycobacteria and related organisms. Proceedings of the National Academy of Sciences of the USA.101(1):314-9. doi: 10.1073/pnas.0305439101.

Quattrocchi, U. (2012). Icacina. In: CRC World Dictionary of Medicinal and Poisonous Plants, CRC Press, Boca Raton, Florida, p. 2055.

Schaeffer, M.L., Agnihotri, G., Volker, C., Kallender, H., and Lonsdale, J. T. (2001). Purification and biochemical characterization of the *Mycobacterium tuberculosis* B-ketoacyl-acyl carrier protein synthases KasA and KasB. Journal of Biological Chemistry. 14;276(50):47029-37. doi: 10.1074/jbc.M108903200.

Sharma, D., and Yadav, J.P. (2016). An overview of phytotherapeutic approaches for the treatment of tuberculosis. Mini Reviews in Medicinal Chemistry, 17: 167–183. doi: 10.2174/1389557516666160505114603.

Tuyiringire, N., Mugisha, I.T., Tusubira, D., Munyampundu, J., Muvunyi, C.M., and Heyden, Y.V. (2022). In vitro antimycobacterial activity of medicinal plants Lantana camara, Cryptolepis sanguinolenta, and Zanthoxylum leprieurii. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 27: 100307. https://doi.org/10.1016/j.jctube.2022.100307.

WHO. (2023). Global tuberculosis report 2023: TB incidence. Available at: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/tb-disease-burden/1-1-tb-incidence.

WHO. (2024). Tuberculosis. Available at: https://www.who.int/news-room/fact-sheets/detail/tuberculosis. (Accessed online: 01st January, 2025).

Wolucka, B.A. (2008). Biosynthesis of D-arabinose in mycobacteria—A novel bacterial pathway with implications for antimycobacterial therapy. FEBS Journal, 275: 2691–2711.