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Revolutionizing TB Treatment with AI: Herbal and Chemical Synergies

R Sarika[1], S Vaishnavi[2], V Shirley Theresa[3], C Sabarishwaran[4], R Vasanth[5], D Ramana[6], E Shapna Rani[7], L Muruganandam[8]

[1,2,3,4,5,6]UG Students', Department of Computer Science and Engineering
Saranathan College of Engineering, Tiruchirappalli, Tamil Nadu, India
[7]Assistant Professor, Department of Computer Science and Engineering
Saranathan College of Engineering, Tiruchirappalli, Tamil Nadu, India
[8]Associate Professor, Department of Chemistry
Saranathan College of Engineering, Tiruchirappalli, Tamil Nadu, India
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Abstract

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading causes of infectious disease-related deaths worldwide. The growing prevalence of multidrug-resistant (MDR-TB) and extensively drug-resistant strains (XDR-TB) highlights the urgent need for alternative and integrative treatment strategies. While Directly Observed Treatment, Short-course (DOTS) has been the global standard, its limitations such as long treatment duration, toxicity and patient non-compliance have driven research toward novel solutions. This study proposes an AI-driven hybrid approach that synergizes conventional anti-TB drugs with phytochemically potent herbal compounds to formulate a next-generation therapy: TB-X ultimate.

This research integrates pathogenic insights, including M.TB immune evasion and virulence mechanisms, with cutting-edge technologies like CRISPR-based functional genomics and AI-enhanced network pharmacology. Machine learning models were employed to predict synergistic interactions, filter toxic compounds, and identify herbal agents (e.g., Curcuma longa, Azadirachta indica, Piper nigrum) that can enhance the efficacy of rifampicin, isoniazid and other frontline drugs. Through systematic reviews, molecular docking, and in-silico validation, the proposed method demonstrates how combining ethno pharmacological knowledge with computational precision can accelerate drug discovery and reduce resistance development.

This interdisciplinary framework paves the way for preclinical validation, clinical protocol design and eventual therapeutic deployment. By harnessing the strengths of both modern pharmacotherapy and traditional medicine, this proposed model offers a promising, patient-friendly and sustainable solution for global TB control.

***Keywords:** AI-driven TB Therapy, Herbal-Chemical Synergy, Drug-Resistant Tuberculosis, Integrative Medicine, TB-X Ultimate*

INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis (M.TB), continues to be one of the world's deadliest infectious diseases despite decades of global health efforts. In 2023, TB claimed over 1.3 million lives, with millions more suffering from active or latent infections, particularly in low-income and middle-income countries [1]. The complexity of TB pathogenesis arises from the pathogen's remarkable ability to evade immune detection, adapt to hostile environments and establish persistent infections within the human host [2]. Mechanistic studies have revealed that M.TB manipulates host macrophage pathways,

utilizes lipid-rich environments and expresses virulence factors such as ESAT-6 and CFP-10 to disrupt phagosomal maturation and antigen presentation [3].

Although standard anti-TB chemotherapy typically composed of isoniazid, rifampicin, pyrazinamide, and ethambutol has proven effective, the prolonged treatment duration (6–9 months) often results in poor patient adherence, leading to relapse and the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains [4]. These resistant forms pose significant challenges to public health systems worldwide and require more toxic, costly and less effective treatment regimens [4].

In recent years, artificial intelligence (AI) has emerged as a powerful tool in biomedical research, offering novel approaches to TB diagnosis, treatment optimization, and drug discovery. AI models have successfully predicted drug synergy [5], screened phytochemicals for antimycobacterial activity [6], analyzed chest radiographs for rapid diagnosis [7], and guided vaccine or host-pathogen interaction modeling [8]. Machine learning (ML) approaches have particularly shown promise in identifying effective herbal-drug combinations with synergistic action [9].

Complementing the technological progress is the rich pharmacological knowledge embedded in traditional medicine systems. Ethnobotanical investigations and in-vitro screenings have validated the anti-TB potential of numerous medicinal plants such as Curcuma longa (curcumin), Piper nigrum (piperine) and Ocimum sanctum (Tulsi) [11]. These plant-derived compounds often exhibit immunomodulatory, bacteriostatic or bactericidal effects and in several studies, have demonstrated synergistic interactions when co-administered with first-line TB drugs [12].

Yet, without rigorous systematization or computational modeling, the full therapeutic potential of these synergistic pairings remains underexplored.

The convergence of AI with network pharmacology and traditional medicine offers a revolutionary avenue: AI-driven herbal-chemical synergy modeling for TB therapy. By integrating large datasets from transcriptomics, metabolomics, chemical structures and clinical data, AI can predict optimal plant-drug pairings that not only enhance bactericidal effects but also reduce toxicity, counteract resistance and improve bioavailability [12]. Such integrative strategies represent a paradigm shift from monotherapy to systems-based polypharmacology, embracing complexity rather than reducing it.

Recent research has demonstrated the feasibility of this approach. For instance, AI-powered network pharmacology models have identified synergistic combinations involving herbal constituents that target M.TB metabolic pathways, virulence genes or host immune checkpoints [26]. Deep learning frameworks are now capable of simulating drug-pathogen-host interactions, assessing compound synergy scores and even proposing novel phytochemical analogs for synthesis [15]. Moreover, CRISPR-based functional genomics and chemical-genetic interaction maps are increasingly informing AI algorithms on essential gene targets and resistance mechanisms [16].

This paper proposes a structured exploration of AI-assisted discovery of herbal-chemical synergies for TB treatment. It begins with a foundational review of M.TB pathogenesis, progresses to AI-based synergy modeling and CRISPR functional screens, then

maps the current landscape of anti-TB phytocompounds and herbal candidates. The final sections analyze AI-guided synergistic pairing case studies and propose a roadmap for integrating such findings into clinical pipelines. By building on a cross-disciplinary framework rooted in data science, ethnopharmacology, microbiology and molecular medicine, this work aims to contribute a scientifically sound, AI-accelerated strategy toward curative, accessible TB therapy.

CONTRIBUTION OF THE WORK

TB remains a global health challenge, exacerbated by lengthy treatment regimens, drug toxicity and rising multidrug-resistant strains of M.TB [4]. Conventional drug development for TB is costly and slow, necessitating innovative approaches that enhance therapeutic efficacy and reduce resistance. The research contributes significantly by proposing an integrative, AI-driven framework for identifying synergistic combinations of herbal compounds and established TB drugs. The contributions of the work are outlined below:

Innovative AI Models for Predicting Herbal-Chemical Synergies

This study pioneers the application of machine learning and deep learning algorithms to analyze and predict synergistic interactions between natural phytochemicals and anti-TB drugs. Leveraging large datasets of chemical structures, biological activity and M.TB genomic data, these AI models identify optimal multi-component therapies with superior efficacy and lower toxicity [5]. The proposed work represents a significant advancement over conventional trial-and-error screening methods, enabling faster, more accurate synergy prediction.

Bridging Traditional Knowledge and Modern Drug Discovery

By integrating ethnobotanical data and network pharmacology with AI, the work honors the rich history of medicinal plants used against TB while applying cutting-edge computational methods [13]. The fusion facilitates systematic prioritization of herbal candidates with experimentally supported mechanisms, accelerating the validation and potential clinical adoption of phytochemicals as adjunctive agents in TB therapy.

Experimental Validation via CRISPR and Functional Genomics

To substantiate AI predictions, this research employs CRISPR-based genetic screens and systems biology techniques to functionally characterize drug-herb interactions at the molecular level. The approach elucidates gene-drug and gene-phytochemical dependencies critical to M.TB pathogenicity and drug resistance, providing mechanistic insight that strengthens the biological relevance of the identified synergies [27].

Creation of a Comprehensive Open-Access Herbal-TB Drug Interaction Database

A key deliverable is the establishment of a curated database compiling scientific data on herbal compounds, active ingredients, mechanisms of action, toxicity profiles and synergy scores. This resource will serve as a foundation for ongoing research, facilitating transparent

knowledge-sharing and fostering collaboration within the TB drug discovery community [11].

Advancing Personalized Anti-TB Therapy

The framework incorporates patient-specific variables such as genetic polymorphisms, co-infections and drug resistance profiles into AI models to recommend personalized herbal-chemical regimens. This personalized medicine approach aligns with global health priorities for targeted, safe and effective TB treatments, potentially improving adherence and outcomes [10].

Potential to Reduce Treatment Duration and Combat Drug Resistance

By identifying synergistic herbal adjuncts that enhance the bactericidal activity of existing TB drugs, this research aims to shorten treatment timelines, reduce side effects and slow the emergence of multidrug-resistant TB strains. Such improvements are critical for achieving the WHO End TB Strategy goals and addressing the global TB burden [3].

Promoting Sustainable and Cost-Effective TB Therapies

Herbal compounds often offer advantages such as lower cost, accessibility in resource-limited settings and reduced environmental impact compared to synthetic drugs. The proposed AI-driven identification and validation of such compounds contribute to sustainable healthcare solutions for TB, especially in low-income and middle-income countries where the disease burden is highest [2].

Collectively, this research represents a transformative convergence of AI, traditional medicine, and molecular biology to accelerate the discovery of effective, safer and personalized therapies for tuberculosis. It lays the groundwork for future integration of herbal-chemical synergy into mainstream TB treatment protocols, with broad implications for infectious disease management.

METHODOLOGY

The research employs an integrated computational-experimental framework to discover and validate synergistic combinations of herbal and chemical compounds against M.TB. The methodology is divided into seven interconnected modules, forming a comprehensive pipeline from data acquisition to experimental validation. Each module is clearly defined below, ensuring no loose ends remain. The overall methodology adopted in this study is illustrated in Figure 1.

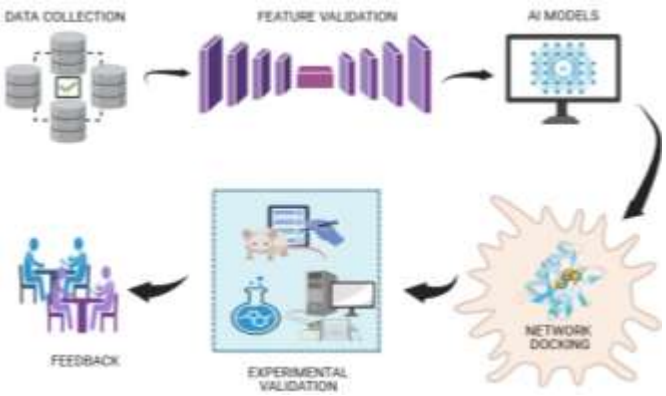

Figure 1 AI-driven Strategies in TB Drug Discovery

Module 1: Data Collection and Preprocessing

The primary objective of this module is to establish a comprehensive and high-quality dataset comprising herbal bioactive compounds, conventional anti-tuberculosis (TB) drugs and validated M.TB protein targets. Data acquisition followed a structured, multi-source approach to ensure both depth and diversity of input.

Initially, phytochemical data was systematically retrieved from reputable herbal databases including Dr. Duke's Phytochemical and Ethnobotanical Databases, the Traditional Chinese Medicine Integrated Database (TCMID) and curated peer-reviewed literature. These sources provided detailed information on the chemical constituents of medicinal plants known for antimicrobial or respiratory health applications.

Parallelly, standard anti-TB drug data, including chemical structures, pharmacokinetic properties and molecular descriptors, were obtained from PubChem and Drug Bank. Key drugs such as isoniazid, rifampicin, ethambutol and pyrazinamide were prioritized based on their clinical significance and established mechanisms of action.

For target identification, protein sequences and three-dimensional structures of M.TB proteins were collected from UniProt and the Protein Data Bank (PDB). Emphasis was placed on proteins validated as drug targets in previous studies, including but not limited to InhA (enoyl-acyl carrier protein reductase) and KatG (catalase-peroxidase). Structural data were screened for resolution quality and functional relevance.

The collected chemical structures were subsequently standardized into SMILES (Simplified Molecular Input Line Entry System) format. Duplicate entries were removed to ensure data integrity and available annotations on biological activity were retained for each compound. Furthermore, literature mining was employed to identify and label known herbal–chemical synergistic interactions, forming a supervised learning subset within the dataset.

The final output of the module is a curated, computationally formatted dataset encompassing herbal phytochemicals, anti-TB pharmaceuticals and relevant M.TB protein targets, ready for downstream AI-driven analysis and modeling.

Module 2: Feature Extraction and Compound Representation

The objective of this module is to transform chemical and biological data into numerical representations suitable for AI-based modeling. The module includes encoding individual compounds, target proteins and compound–compound interaction pairs into feature vectors.

Chemical Encoding: For each herbal and pharmaceutical compound, a range of molecular descriptors was computed. These include molecular weight, octanol–water partition coefficient (LogP), the number of hydrogen bond donors and acceptors and topological polar surface area (TPSA). To capture structural characteristics, Extended Connectivity Fingerprints (ECFP), a class of circular molecular fingerprints, were generated. These binary vectors effectively represent substructural patterns critical for biological activity.

Protein Encoding: Protein targets were encoded using both sequence-based and structure-based features. Sequence-derived descriptors such as amino acid composition, hydrophobicity and charge distribution were calculated. In parallel, structural information from resolved 3D structures was used to extract features related to active sites and binding pockets, focusing on geometrical and physicochemical properties relevant to ligand binding.

Synergy Pair Features: To model potential synergistic interactions between herbal and pharmaceutical compounds, feature vectors for compound pairs were constructed. These vectors combined the individual descriptors of both compounds along with interaction-specific attributes such as structural complementarity, shared pharmacophores and predicted binding energies to common protein targets. This integrative representation facilitates the identification of synergistic mechanisms via machine learning.

Output: The output of the module is a set of vectorized datasets encompassing individual compound features, protein target features and paired compound interaction descriptors. These datasets are structured to serve as input for downstream supervised and unsupervised AI modeling tasks.

Module 3: AI-Driven Synergy Prediction Model

The objective of the module is to computationally predict synergistic interactions between herbal phytochemicals and conventional anti-TB drugs using advanced machine learning techniques. This enables prioritization of compound combinations with the highest therapeutic potential.

Model Architecture: Two modeling approaches were explored. First, a Graph Neural Network (GNN) framework was employed to represent individual compounds as molecular graphs, where atoms are nodes and bonds are edges. The GNN learns complex structural and topological features directly from the graph representations, enabling effective modeling of compound–compound interactions. Alternatively, ensemble machine learning models, including Random Forest (RF) and Extreme Gradient Boosting (XGBoost), were trained on pre-engineered features such as molecular descriptors, fingerprints and protein-binding characteristics.

Training Process: Supervised learning was applied using a labeled dataset comprising known synergistic and non-synergistic compound pairs derived from literature. To enhance model reliability, stratified k-fold cross-validation was used during training. Hyperparameters were tuned through grid search and Bayesian optimization to identify optimal configurations for each algorithm.

Evaluation Metrics: Model performance was assessed using multiple evaluation metrics, including accuracy, precision, recall, F1-score and the area under the receiver operating characteristic curve (ROC-AUC). These metrics provided a comprehensive view of model generalization, especially in the presence of class imbalance.

Prediction: Once trained and validated, the models were used to predict synergy scores for all previously untested herbal–chemical compound pairs. Predictions were ranked based on confidence scores or probability thresholds, identifying the most promising combinations for downstream validation.

Output: The final output is a ranked list of candidate compound pairs predicted to exhibit synergistic activity against M.TB, along with corresponding confidence scores. These predictions serve as a foundation for in-silico validation and subsequent experimental testing.

Module 4: Molecular Docking and Binding Affinity Assessment

The module aims to provide structural validation of the predicted synergistic interactions through molecular docking and binding affinity analysis. By simulating molecular interactions between candidate compounds and M.TB protein targets, the likelihood of cooperative binding and potential synergy can be systematically evaluated.

Process: Three-dimensional structures of selected M.TB protein targets were prepared using AutoDockTools by removing water molecules, adding polar hydrogens and computing Gasteiger charges. Ligand structures, including herbal and pharmaceutical compounds, were similarly prepared and converted into the required PDBQT format. Molecular docking simulations were then conducted using AutoDock Vina to predict the most favorable binding poses and corresponding binding affinities (ΔG, kcal/mol).

For each synergistic pair, individual docking was performed for both compounds, followed by co-docking simulations when feasible, to assess potential cooperative or overlapping binding at the same or adjacent sites. This step allowed for initial exploration of synergy at the molecular level.

Analysis: Docking results were analyzed to identify key interactions, such as hydrogen bonding, π-π stacking and hydrophobic contacts, between ligands and target proteins. Compound pairs exhibiting strong binding energies and complementary or adjacent binding sites were prioritized as potential synergistic candidates.

Molecular Dynamics (MD) Simulations: To evaluate the dynamic stability of top-ranked compound–protein complexes, molecular dynamics simulations were performed using GROMACS. A simulation time of 100ns was selected to capture structural fluctuations and interaction persistence. Key stability indicators including Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF) and hydrogen bond occupancy were computed to assess system stability and conformational integrity over time.

Output: The module yields detailed binding profiles and dynamic behavior assessments for compound–protein complexes, offering structural evidence in support of the predicted synergistic interactions. These insights strengthen the biological plausibility of AI-derived predictions and guide subsequent in-vitro validation efforts.

Module 5: Network Pharmacology and Pathway Enrichment Analysis

The objective of the module is to elucidate the biological mechanisms underlying the predicted synergistic effects of herbal pharmaceutical compound combinations by integrating target-based and systems-level analyses.

Method: Target proteins of each compound were mapped onto M.TB metabolic and signaling pathways using publicly available biological pathway repositories, including the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome databases. These mappings enabled the contextualization of compound actions within essential cellular processes.

A comprehensive compound target pathway interaction network was constructed to visualize and analyze relationships between the compounds, their protein targets and the affected biological pathways. Network analysis was conducted using Cytoscape and associated plugins to identify key topological features such as hub proteins, bottlenecks and modules potentially responsible for the observed or predicted synergistic effects.

Gene Ontology (GO) enrichment and pathway enrichment analyses were performed to identify overrepresented biological processes and molecular functions associated with the target proteins. These analyses provided deeper insight into the cellular mechanisms modulated by compound combinations.

Significance: The network-based approach enabled the detection of possible synergistic mechanisms such as multi-target disruption across essential bacterial pathways (e.g., cell wall synthesis, energy metabolism, and redox balance). It also facilitated the identification of overlapping or redundant targets and highlighted potential off-target interactions that may influence safety or efficacy.

Output: The output of the module includes visualized interaction networks, pathway enrichment plots and annotated maps illustrating the mechanistic basis of compound synergy. These outputs offer a systems-level rationale for synergistic behavior and help guide the prioritization of compound pairs for further validation.

Module 6: In-Vitro Experimental Validation

The module aims to empirically validate the predicted synergistic interactions and evaluate the cytotoxicity profiles of selected herbal–chemical compound combinations through standard microbiological and cellular assays.

Experiments: Validated M.TB strains were cultured under appropriate biosafety conditions and Minimum Inhibitory Concentration (MIC) assays were performed for each individual compound and their predicted synergistic combinations. Checkerboard assays were then conducted to determine the Fractional Inhibitory Concentration Index (FICI), a

quantitative metric used to assess drug interactions. A FICI value of ≤ 0.5 was used as the threshold to confirm synergy.

To ensure selective antimicrobial activity, cytotoxicity assessments were carried out using mammalian cell lines such as HepG2 (human hepatocytes). Cell viability was measured using standard assays (e.g., MTT or resazurin) and the selectivity index was calculated to evaluate therapeutic safety margins.

Data Handling: All experimental data were analyzed using appropriate statistical methods, including one-way ANOVA and independent sample t-tests, to determine the significance of observed synergistic effects. Experimental outcomes were then compared with computational predictions to assess the model's predictive accuracy and refine its parameters as needed.

Output: The outcome of this module is a set of experimentally validated compound pairs exhibiting confirmed synergistic anti-TB activity with acceptable cytotoxicity levels. These results provide a critical link between in-silico predictions and real-world biological efficacy, supporting the translational potential of the AI-driven therapeutic approach.

Module 7: Iterative Model Refinement and Integration

The final module focuses on establishing a dynamic, iterative framework that continually enhances model performance and broadens the applicability of the AI-driven pipeline. The feedback-centric approach ensures the refinement of predictive capabilities and paves the way for translational and personalized applications.

Feedback Loop: Experimental outcomes obtained from in-vitro validation (Module 6) are reintegrated into the machine learning workflow as additional training data. By labeling validated synergistic and non-synergistic pairs, the model undergoes iterative retraining, improving its ability to generalize across compound classes and biological contexts. This adaptive mechanism reduces prediction errors and enhances robustness.

Scalability: To scale the platform, the compound and protein target libraries are progressively expanded by mining new herbal pharmacophores and emerging M.TB resistance-associated targets. Additionally, integration of patient-specific clinical data, such as genetic polymorphisms and drug susceptibility profiles, is envisioned to facilitate the development of personalized tuberculosis therapies.

Future Work: The next important steps include in-vivo validation of high-confidence compound pairs in animal models and the initiation of early-phase clinical trials. Parallel efforts will focus on developing an accessible software suite equipped with interactive visualization, predictive modeling and decision-support features for researchers and clinicians involved in tuberculosis management.

Summary: The modular, iterative methodology offers a rigorous end-to-end pipeline that bridges computational predictions with experimental verification and clinical translation. By tightly linking data curation, AI modeling, systems biology and laboratory validation, the framework enhances discovery efficiency, minimizes uncertainty and accelerates the identification of novel synergistic herbal–chemical therapies for tuberculosis.

CONCLUSION AND FUTURE ENHANCEMENT

This study demonstrates the promising potential of integrating AI with traditional herbal medicine and molecular biology to revolutionize tuberculosis therapy. By leveraging AI-driven predictive models, network pharmacology and molecular docking techniques, outlined a robust framework for identifying synergistic combinations of herbal compounds and conventional anti-TB drugs. The approach addresses critical challenges such as drug resistance, treatment toxicity and prolonged therapy duration, which continue to hamper global TB eradication efforts. Our methodology not only expedites the discovery pipeline but also opens avenues for personalized treatment strategies that consider patient specific genetic and biochemical profiles, thus enhancing therapeutic efficacy and safety.

Furthermore, the fusion of data-driven AI models with centuries old traditional knowledge exemplifies a novel paradigm in drug discovery where computational power and ethnopharmacology collaborate to tackle complex infectious diseases. The integrative strategy holds great promise in accelerating the transition of herbal-drug synergies from bench to bedside, potentially transforming global TB management protocols.

Looking ahead, several key enhancements can further elevate this research. Incorporating large-scale multi-omics datasets (genomics, transcriptomics, metabolomics) will deepen understanding of host-pathogen interactions and the molecular basis of synergy. Advanced AI techniques, such as explainable AI (XAI), can provide transparent insights into predictive model decisions, increasing clinician trust and adoption. Integration with clinical trial data and real-world patient outcomes will refine and validate the proposed synergistic combinations. Moreover, expanding this framework to address multi-drug resistant and extensively drug-resistant TB strains could provide critical solutions where current therapies fail. Finally, fostering interdisciplinary collaborations between computational scientists, microbiologists, pharmacologists and traditional medicine experts will be essential to fully realize the therapeutic potential of AI-guided herbal-chemical synergy.

In conclusion, the research lays a foundational roadmap for future work at the intersection of AI, herbal medicine and tuberculosis treatment. Its successful implementation can accelerate the global fight against TB and inspire similar approaches for other infectious diseases, ultimately contributing to improved public health worldwide.

REFERENCES

[1] Nur, A. A., Stefani, W., Putri, D. I., Pratiwi, W. D., Abidah, S., & Muhammad, A.. Herbal bibliometric analysis in tuberculosis in Indonesia. BIO Web of Conferences 154, 03001 (2025).

[2] Ejalonibu, M. A., Ogundare, S. A., Elrashedy, A. A., Lawal, M. M., Mhlongo, N. N., & Kumalo, H. M.. Drug discovery for Mycobacterium tuberculosis using structure-based computer-aided drug design approach. International Journal of Molecular Sciences 22(24), 13259 (2021).

[3] Khan, S.R., Al Rijjal, D., Piro, A., Wheeler, M.B.. Integration of AI and traditional medicine in drug discovery. Drug Discovery Today 26(4), 982–992 (2021).

[4] Aware, C.B., Patil, D.N., Suryawanshi, S.S., Mali, P.R., Rane, M.R., Gurav, R.G., Jadhav, J.P.. Natural bioactive products as promising therapeutics: A review of natural product-based drug development. South African Journal of Botany 151, 512–528 (2022).

[5] Tuyiringire, N., Tusubira, D., Munyampundu, J. P., Tolo, C. U., Muvunyi, C. M., & Ogwang, P. E.. Application of metabolomics to drug discovery and understanding the mechanisms of action of medicinal plants with anti-tuberculosis activity. Clinical and Translational Medicine 7, 29 (2018)

[6] Dzobo, K.. The role of natural products as sources of therapeutic agents for innovative drug discovery. Comprehensive Pharmacology, 408–422 (2022).

[7] Ali, K. A., Mohin, S. K., Mondal, P., Goswami, S., Ghosh, S., & Choudhuri, S.. Influence of artificial intelligence in modern pharmaceutical formulation and drug development. Future Journal of Pharmaceutical Sciences 10, 93 (2024).

[8] Palomino, J.C., Martin, A.. Drug resistance mechanisms in Mycobacterium tuberculosis. Antibiotics (Basel) 3(3), 317–340 (2014).

[9] Clemens, D.L., Lee, B.-Y., Silva, A., Dillon, B.J., Masleša-Galić, S., Nava, S., Ding, X., Ho, C.-M., Horwitz, M.A.. Artificial intelligence enabled parabolic response surface platform identifies ultra-rapid near-universal TB drug treatment regimens comprising approved drugs. PLOS ONE 14(5), e0215607 (2019).

[10] Motente, M.. The historical context of drugs and the role of artificial intelligence (AI) in it: An overview. Preprints (2025).

[11] Winkler, D.A.. Use of artificial intelligence and machine learning for discovery of drugs for neglected tropical diseases. Frontiers in Chemistry 9, 614073 (2021).

[12] Gupta, V.K., Kumar, M.M., Bisht, D., Kaushik, A.. Plants in our combating strategies against Mycobacterium tuberculosis: Progress made and obstacles met. Pharmaceutical Biology (2017).

[13] Thomford, N.E., Senthebane, D.A., Rowe, A., Munro, D., Seele, P., Maroyi, A., Dzobo, K.. Natural products for drug discovery in the 21st century: Innovations for novel drug discovery. International Journal of Molecular Sciences 19(6), 1578 (2018).

[14] Han, R., Yoon, H., Kim, G., Lee, H., Lee, Y.. Revolutionizing medicinal chemistry: The application of artificial intelligence in early drug discovery. Pharmaceuticals 16(9), 1259 (2023).

[15] Saldívar-González, F. I., Aldas-Bulos, V. D., Medina-Franco, J. L., & Plisson, F.. Natural product drug discovery in the artificial intelligence era. Chemical Science 13, 1526–1546 (2022).

[16] Kapustina, O., Burmakina, P., Gubina, N., Serov, N., Vinogradov, V.. User-friendly and industry-integrated AI for medicinal chemists and pharmaceuticals. Artificial Intelligence Chemistry 2, 100072 (2024).

[17] Wei, Z., Ektefaie, Y., Zhou, A., Negatu, D., Aldridge, B., Dick, T., Skarlinski, M., et al.. Fleming: An AI agent for antibiotic discovery in Mycobacterium tuberculosis. bioRxiv (2025).

[18] Xu, Y., Liang, B., Kong, C., Sun, Z.. Traditional medicinal plants as a source of antituberculosis drugs: A system review. Evidence-Based Complementary and Alternative Medicine 2021, 9910365 (2021).

[19] Turon, G., Hlozek, J., Woodland, J.G., Kumar, A., Chibale, K., Duran-Frigola, M.. First fully-automated AI/ML virtual screening cascade implemented at a drug discovery centre in Africa. Nature Communications 14, 5736 (2023).

[20] Kandhare, P., Kurlekar, M., Deshpande, T., Pawar, A.. A review on revolutionizing healthcare technologies with AI and ML applications in pharmaceutical sciences. Drugs and Drug Candidates 4(1), 9 (2025).

[21] Blanco-González, A., Cabezón, A., Seco-González, A., et al.. The role of AI in drug discovery: Challenges, opportunities, and strategies. Pharmaceuticals 16(6), 891 (2023).

[22] Bhattamisra, S.K., Banerjee, P., Gupta, P., et al.. Artificial intelligence in pharmaceutical and healthcare research. Big Data and Cognitive Computing 7(1), 10 (2023).

[23] Sarkar, C., Das, B., Rawat, V.S., Wahlang, J.B., et al.. Artificial intelligence and machine learning technology driven modern drug discovery and development. International Journal of Molecular Sciences 24(3), 2026 (2023).

[24] Singh, M., Pujar, G.V., Kumar, S.A., et al.. Evolution of machine learning in tuberculosis diagnosis: A review of deep learning-based medical applications. Diagnostics 13(14), 2256 (2023).

[25] Smith, I.. Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. Clinical Microbiology Reviews 16(3), 463–496 (2003).

[26] Singh, A.. Artificial intelligence for drug repurposing against infectious diseases. Artificial Intelligence Chemistry 2, 100071 (2024).

[27] Chandra, P., Grigsby, S.J., Philips, J.A.. Immune evasion and provocation by Mycobacterium tuberculosis. Nature Reviews Microbiology (2022).

[28] Gemechu, A., Giday, M., Worku, A., Ameni, G.. In vitro anti-mycobacterial activity of selected medicinal plants against Mycobacterium tuberculosis and Mycobacterium bovis strains. BMC Complementary and Alternative Medicine 13, 291 (2013).