



REVIEW ARTICLE

ARTIFICIAL INTELLIGENCE IN HERBAL TOXICOLOGY: AI-ASSISTED TOXICITY PREDICTION, ADMET ASSESSMENT, HERB–DRUG INTERACTIONS, AND SAFETY EVALUATION

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Article History

Received: 15 December 2025

Revised: 30 January 2026

Accepted: 15 February 2026

Published: 25 March 2026

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ABSTRACT: Herbal medicines represent a valuable source of therapeutically active compounds and are increasingly incorporated into modern healthcare and drug discovery. However, their chemically complex composition, multi-target pharmacological effects, batch-to-batch variability, metabolic transformation, potential toxicity, and herb–drug interactions present significant challenges for systematic safety assessment. Conventional toxicological approaches are often time-consuming, costly, and dependent on extensive experimental studies, highlighting the need for predictive and mechanism-oriented strategies. Artificial Intelligence (AI), including Machine Learning (ML), Deep Learning (DL), and Natural Language Processing (NLP), has emerged as a promising approach for advancing herbal toxicology and safety evaluation. This review critically examines the application of AI-assisted approaches for toxicity prediction, absorption, distribution, metabolism, excretion, and toxicity (ADMET) assessment, herb–drug interaction prediction, mechanistic toxicology, and integrated safety profiling of herbal medicines. Particular attention is given to quantitative structure–activity relationship (QSAR) modelling, molecular docking, virtual screening, pharmacokinetic prediction, multi-omics integration, knowledge graphs, adverse-effect prediction, and explainable AI. These approaches can facilitate the early identification of potentially hazardous phytochemicals, predict organ-specific toxicity, identify toxicophoric structural features, evaluate metabolic liabilities, and characterize interactions with drug-metabolizing enzymes and transporters. Furthermore, integration of chemical, biological, pharmacological, clinical, and toxicological datasets may improve the prioritization of safer herbal candidates and support mechanism-informed risk assessment. Despite these advances, limitations related to data quality, dataset heterogeneity, model interpretability, external validation, uncertainty, and regulatory acceptance remain important challenges. Future integration of explainable AI, standardized toxicological datasets, multi-omics technologies, digital models, and experimental validation could establish more reliable and predictive frameworks for herbal medicine safety evaluation.

Keywords: Artificial Intelligence; Herbal Toxicology; Machine Learning; Deep Learning; Toxicity Prediction; ADMET; Herb–Drug Interactions.

I. INTRODUCTION

1.1 Global Resurgence and Therapeutic Importance of Herbal Medicines

Since ancient times, medicinal plants and natural products have constituted an important foundation of healthcare and remain integral to traditional medical systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani. In recent decades, herbal medicines have experienced a global

resurgence, driven by the increasing prevalence of chronic diseases, growing concerns regarding antimicrobial resistance, and rising interest in natural and holistic therapeutic approaches. Advances in analytical chemistry, molecular biology, pharmacology, and omics technologies have facilitated the identification and characterization of bioactive phytoconstituents and their potential therapeutic targets. Consequently, herbal medicines have attracted considerable attention as sources of pharmacologically active molecules

and potential leads for modern drug development. Despite these advances, the translation of herbal medicines into evidence-based therapeutic systems remains challenging because of their complex and multicomponent nature. Herbal preparations may contain numerous bioactive constituents that can act through multiple molecular targets and biological pathways. Variations in plant species, geographical origin, cultivation conditions, harvesting, processing, extraction procedures, and storage can further contribute to substantial batch-to-batch variability. These factors not only influence therapeutic efficacy but may also affect toxicological profiles and the potential for herb–drug interactions. Therefore, establishing standardized, reproducible, and scientifically validated approaches for evaluating the efficacy and safety of herbal medicines remains an important priority [1].

1.2 Limitations of Conventional Approaches in Herbal Drug Research and Safety Assessment

Conventional herbal drug research, including ethnobotanical investigations, phytochemical characterization, biological screening, and experimental toxicological studies, is often labor-intensive, time-consuming, and resource-intensive. The considerable chemical diversity of medicinal plants further complicates the systematic identification of bioactive and potentially toxic constituents. In addition, differences in extraction methods, phytochemical composition, formulation, and manufacturing processes can result in considerable variability in the pharmacological and toxicological properties of herbal preparations. Traditional experimental screening approaches also have limited throughput and may require extensive in vitro and in vivo investigations before potential safety concerns are recognized. Assessment of absorption, distribution, metabolism, excretion, and toxicity (ADMET), organ-specific toxicity, metabolic liabilities, and herb–drug interactions can therefore become particularly challenging

when numerous phytochemicals are present simultaneously. Furthermore, conventional approaches may have difficulty integrating large and heterogeneous datasets generated from chemical, pharmacological, toxicological, clinical, and omics studies. These limitations have stimulated the development of computational and predictive approaches capable of accelerating herbal drug research while supporting early safety assessment. Artificial Intelligence (AI), Machine Learning (ML), Deep Learning (DL), and Natural Language Processing (NLP) provide emerging tools for analysing complex datasets, predicting toxicity and ADMET properties, identifying potential herb–drug interactions, and elucidating mechanisms underlying therapeutic and adverse effects. The integration of these technologies into herbal toxicology may therefore facilitate a transition from predominantly experimental and reactive safety assessment toward predictive, data-driven, and mechanism-informed evaluation [2].

1.3 The Emerging Role of Artificial Intelligence in Herbal Drug Discovery and Toxicological Safety

Drug discovery has undergone a revolutionary change with artificial intelligence (AI), which can process, integrate, and interpret complex chemical, biological, pharmacological, and toxicological datasets. In herbal research, AI can combine traditional medicinal knowledge with modern pharmacology and toxicology to identify bioactive phytoconstituents while simultaneously evaluating potential safety liabilities. Machine-learning algorithms can recognize patterns associated with activity and toxicity, whereas deep-learning approaches can model nonlinear relationships among compounds, molecular targets, metabolic pathways, and adverse outcomes. Natural language processing can systematically mine ethnobotanical and biomedical literature for reports of adverse effects, contraindications, and herb–drug interactions.

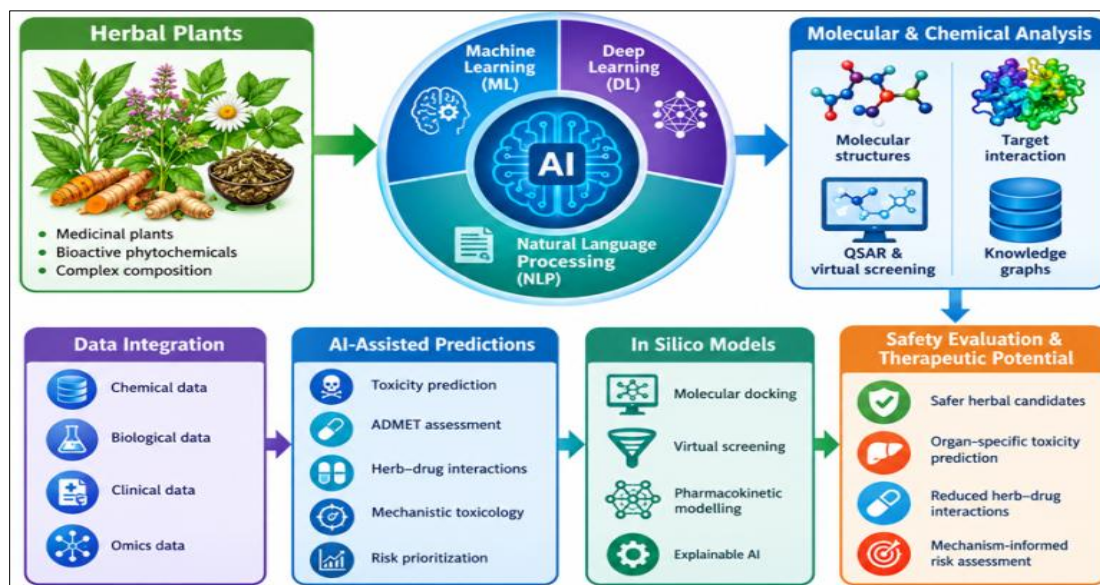


Figure 1: AI-driven herbal drug discovery and safety workflow integrating medicinal plants, molecular structures, multi-omics databases, pharmacological prediction, ADMET profiling, toxicity prediction, and herb–drug interaction assessment. AI can support target identification, mechanism-of-action analysis, safety prioritization, and lead optimization using machine-learning approaches [13].

Molecular docking, network pharmacology, and knowledge graphs can further support mechanistic interpretation of both therapeutic and toxicological interactions. Importantly, AI-enabled ADMET prediction provides an early safety filter by estimating absorption, distribution, metabolism, excretion, and toxicity before extensive experimental testing. Thus, the integration of AI with herbal pharmacology offers a framework in which efficacy, pharmacokinetics, toxicity, and interaction risks can be considered together, supporting safer and more evidence-based development of herbal therapeutics.

2. AI and Machine Learning for Herbal Pharmacology and Toxicology

2.1 Overview of AI, ML, and Deep Learning in Biomedicine

The application of artificial intelligence (AI) to large-scale biological and chemical data is an innovative change in the field of biomedicine, accelerating the drug discovery and development process. The ability of AI to identify patterns, anticipate result, and formulate the hypothesis allows it to bypass the large number of resources and time that is commonly involved in the process of experimentation. In herbal drug discovery, AI provides a mathematical system to analyze multi-component preparations, forecast bioactive components, and evaluate their potency as therapy. Additionally, the use of AI has triggered the creation of innovative virtual screening technologies, drug target discovery plans, and pharmacovigilance approaches to make classical pharmacological procedures consistent with computational rigor [4]. Machine learning (ML), a branch of AI, allows the models to be trained independently based on the data without direct instructions. Regression models and classification schemes are examples of supervised ML algorithms that are regularly used to predict pharmacokinetic properties, drug-likeness features, and molecular features. Herbs with a similar medicinal profile or phytochemical composition are clustered by unsupervised algorithms.

The reinforcement-learning paradigms are used to optimize the bioactivity of drug candidates and reduce their toxicity in a series of steps. The other ML development, called deep learning (DL), extends multilayered neural networks in capturing nonlinear interactions among compounds, targets, and disease pathways in order to explain synergistic phenomena in their complex herbal preparations. The redefinition of personalized medicine is simultaneously being applied to the area of biomedicine with the use of AI and ML. With the help of pharmacogenomic data, electronic health records, and personalized omics data, AI can adjust herbal or traditional treatments to the physiological and genetic characteristics of individuals. This is a precision-yet-strategy, which increases treatment effectiveness and reduces safety risks. Moreover, AI gathers heterogeneous data and conducts real-time literature mining, which makes drug-discovery processes consistent with the recent scientific advancement. The intersection of AI, ML, and DL is consequently transforming old and herbal research, creating the data-driven, scalable, and effective methodological paradigms.

2.2 Common Algorithms Used (e.g., Random Forests, SVM, CNNs, RNNs)

Random Forests (RF) are ensemble learning algorithms that build many decision trees during training to predict outcomes more correctly than single trees. Drug development uses RF models to predict phytochemical bioactivity, screen drug-likeness, and assess pharmacokinetic and toxicity. Herbal research, where thousands of chemicals with different structural motifs must be analysed concurrently, is best done with them because they resist overfitting and handle large-dimensional data. RF also gives feature-importance ratings to assist researchers find bioactive molecular descriptors. SVMs are supervised learning models that classify data points by finding an ideal hyperplane in multidimensional space. SVMs in pharmacology can classify active and inactive compounds, measure binding affinities, and find therapeutic targets. By modelling complicated nonlinear limits with kernel functions, they can separate bioactive compounds in herbal medicine development and work effectively with small-to-medium data. SVMs prioritise phytochemicals by predictive significance to speed up experimental validation. CNNs and RNNs are deep learning models that can represent complicated, high-dimensional data. CNNs may query ligand-target interactions using spatial and structural data, such as molecular graphs or three-dimensional conformations, to create accurate predictions. Herbal medicine-induced metabolic pathway or gene expression time-series analysis. When coupled with other algorithmic approaches, RNNs, which represent sequential data, aid time-series analysis in gene expression studies. These designs provide the framework for predicting novel treatment possibilities [5].

2.3 The use of the Big Data and Omics to improve AI Models.

Biological research produces large, diverse data such as genomes, proteomics, metabolomics, and clinical data. AI may extract embryonic knowledge of molecular connections, disease processes, and pharmacological activities from these datasets, revealing novel treatment targets. Combining multi-source data on herbal drug development, multi-component formulations, interactions, and therapeutic usage gives a complete picture. On several biological scales, omics technologies provide comprehensive cellular molecular profiling. Genomics describes genetic variants that impact medication response, proteomics protein interactions and signal pathways, and metabolomics small molecules and metabolites affected by therapy. AI algorithms predict herbal medication pharmacodynamics, pharmacokinetics, and toxicity using these omics datasets. Multi-omics data may improve bioactive chemical identification and mechanism of action prediction. Big data, omics, and AI will enable precision herbal treatments. Integrating ethnopharmacological, environmental, and patient-specific omics profiles predicts personalised therapeutic responses using machine learning. Thus, AI, big data, and omics will improve herbal medicine research by building empirical, predictive, and effective methods.

Topic	Description	Key Applications in Drug Discovery	Advantages
 AI, ML, and Deep Learning	Computational frameworks that mimic human intelligence (AI), learn patterns from data (ML), and capture complex non-linear relationships using multi-layered neural networks (DL).	- Automates data analysis of biological/chemical datasets - Predicts bioactivity - Identifies potential drug targets - Supports personalized medicine	- Accelerates research - Improves predictive accuracy - Reduces experimental costs - Enables rational design of multi-component therapeutics
 Common Algorithms	Widely used algorithms include Random Forests (RF), Support Vector Machines (SVM), Convolutional Neural Networks (CNNs), and Recurrent Neural Networks (RNNs), each optimized for specific data types.	RF: Bioactivity prediction and feature importance identification SVM: Classification of active/inactive compounds CNNs: Molecular structure and image analysis RNNs: Time-series or sequential biological data	- High predictive performance - Flexibility in handling diverse datasets - Ability to capture structural and temporal patterns - Robustness against overfitting
 Role of Big Data and Omics	Integration of large-scale datasets from genomics, proteomics, metabolomics, and clinical sources to inform AI models.	- Identifies bioactive compounds - Provides mechanistic insights - Reveals multi-target interactions - Enables personalized therapeutic predictions	- Enhances accuracy and reliability of predictions - Supports multi-omics integration - Facilitates precision medicine - Provides mechanistic understanding of drug actions

Figure 2: Overview of AI and Machine Learning Tools in Drug Discovery [43-46].

3. AI-Driven Approaches in Herbal Drug Discovery and Safety Assessment.

3.1 In Silico Screening of Herbal Compounds

In silico screening is a computational approach that rapidly evaluates thousands of phytochemicals from medicinal plants to identify compounds with potential therapeutic activity. Artificial intelligence (AI) and machine learning prioritize promising molecules based on their structural and physicochemical properties, reducing the need for extensive laboratory screening. Selected compounds are then subjected to virtual docking, where their interactions with specific disease-related protein targets are simulated to predict the most favorable binding orientation. Binding affinity analysis quantifies the strength and stability of these interactions, enabling researchers to rank herbal compounds according to their predicted efficacy [6]. Molecular modeling, including molecular dynamics simulations, further examines the stability, flexibility, and conformational changes of the protein–ligand complex under physiological conditions. Together, these computational techniques accelerate herbal drug discovery by improving lead identification, reducing development costs and time, minimizing experimental failures, and supporting the rational design of safe, effective, and evidence-based phytopharmaceutical candidates for further experimental validation [7].

3.2 Virtual Docking, Binding Affinity, and Molecular Modelling.

Virtual docking and molecular modelling are key tools in this sector. Docking approaches estimate the optimal ligand binding position, improve scoring functions, predict conformational flexibility, and optimise docking poses to understand pharmacological action. Artificial intelligence that utilises prior experiment data to improve predictions supports

these methods. Bioactivity predictions are correct because molecular dynamics simulations establish ligand-target complex stability in physiological conditions. AI-assisted virtual docking can quickly scan large phytochemical datasets, unlike previous techniques. Machine-learning techniques improve binding-affinity estimates, reducing false positives and identifying the most promising candidate medications. AI-based molecular modelling may also anticipate the synergistic effects of more than two herbal elements, which is significant for multi-component herbal preparations [8-9].

Virtual docking for herbal medicine development is expanding rapidly. AI-enhanced docking predicts flavonoids' antiviral, alkaloids' anticancer, and terpenoids' neuroprotective properties. These methods help pick candidates and give mechanistic insights for rational herb design and optimisation. Traditional herbal knowledge and current pharmaceuticals are linked via AI-based molecular modelling [10-11].

3.3 AI-Based QSAR, ADMET, and Toxicity Prediction of Phytochemicals.

Quantitative structure–activity relationship (QSAR) models relate chemical structure and molecular descriptors to biological outcomes and can be adapted for early toxicological screening of phytochemicals. AI-based QSAR models using Random Forests, Support Vector Machines, and Deep Neural Networks can predict multiple pharmacological and toxicological endpoints and prioritize compounds for experimental validation. A central component of this process is absorption, distribution, metabolism, excretion, and toxicity (ADMET) assessment. AI models trained on pharmacokinetic and toxicological datasets can estimate solubility, permeability, metabolic stability, transporter liability, enzyme-mediated metabolism, and potential toxicity. For herbal

medicines, these predictions are particularly valuable because multiple constituents may contribute to efficacy as well as adverse effects. Toxicity-oriented models can screen for toxicophoric structural features and potential hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, genotoxicity, and cytotoxicity. Combining QSAR with ADMET and mechanistic information therefore allows candidate phytochemicals to be ranked not only by predicted therapeutic activity but also by their potential safety liabilities, reducing late-stage attrition and supporting rational preclinical safety assessment [12].

3.4 The De Novo Drug Designing of Herbal Leads via AI

De novo drug design employs AI algorithms to synthesise new chemicals with desired biological activity. VAEs, GANs, and reinforcement-learning-based generative models provide novel substances in herbal medication development. These methods provide safer and more effective phytochemical analogues. These models include molecular scaffolds, bioactivity, and pharmacokinetic limitations to generate chemically optimised molecules. AI-based de novo design expands the chemical space beyond phytochemicals and allows for bioactive analogues. With virtual screening and molecular docking, ADMET characteristics, target selectivity, and binding affinity may be examined rapidly, speeding lead optimization. AI-based de novo synthesis of herbal-inspired compounds has

been successful in herbal indications like cancer, neurodegenerative diseases, and infections. AI systems use ethnopharmacological evidence to realise that de novo designs are mostly based on traditional knowledge and may be used in modern drug-development processes. The next-generation, data-driven, high-throughput, and accurate herbal medicine design is AI-based [14-15].

4. Data Mining and Knowledge Graphs from Traditional Medicine

4.1 NLP and Text Mining in Ayurveda, TCM, and Ethnobotanical Databases

Natural science has changed knowledge extraction from traditional conventional medicine literature like Ayurveda, TCM, and Ethnobotanical database. The quantity of unstructured data on plant species, preparation, dose, medicinal use, and clinical effectiveness is calculated using NLP and text-mining algorithms. Again, AI-based solutions are needed since curating this material by hand is tiresome, time-consuming, and laborious. NLP algorithms can automatically extract, normalise, and format such data to create searchable databases for herbal medication identification.

Table 1: Case Studies of AI Platforms Mining Traditional Herbal Knowledge			
Platform / Study	Methodology / AI Approach	Application / Focus	Key Findings / Outcomes
TCM-KG	Knowledge graph + NLP + machine learning	Mining Traditional Chinese Medicine literature for herb-compound-target-disease associations	Identified novel compound-target interactions and predicted synergistic herb combinations for cardiovascular and anticancer therapies [38]
AyurvedaNLP	NLP + Named Entity Recognition + Relation Extraction	Extraction of herb-disease associations from classical Ayurveda texts	Curated large-scale, structured datasets linking phytochemicals to therapeutic indications; prioritized anti-inflammatory and neuroprotective herbs [39]
HERB Database Platform	AI-based text mining + data integration	Consolidation of ethnobotanical and biomedical literature for herbal bioactivity prediction	Enabled high-throughput identification of bioactive phytochemicals and multi-target interactions; facilitated virtual screening of candidate compounds [40]
TCM Database@Taiwan AI Module	NLP + Deep Learning + Network Analysis	Predict bioactive compounds and multi-target effects of TCM herbs	Predicted pharmacological effects of flavonoids and terpenoids; validated synergistic combinations; guided experimental prioritization [41]
Ayurveda Knowledge Graph (AyKG)	Ontology + Semantic network + Machine learning	Integration of Ayurvedic phytochemical knowledge with modern pharmacology	Revealed novel herb-drug interactions, potential ADMET profiles, and multi-target therapeutic leads; supported rational herbal drug discovery [42]
DeepEthnoHerb	Deep learning + NLP + Knowledge graph	Mining ethnobotanical literature across multiple regions	Identified cross-cultural herb similarities, bioactive compounds, and potential therapeutic targets; facilitated global herbal lead prioritization [43]

Named entity identification, connection extraction, and topic modelling uncover correlations between molecular targets, phytochemicals, herbs, and clinical symptoms. AI may also search old Ayurvedic literature for plants with anti-inflammatory or neuroprotective qualities and compare them to contemporary pharmacological data. These techniques will let scientists integrate ethnopharmacological knowledge with computational drug-discovery procedures to rank promising herbal hits. Recent natural-language processing and machine-learning studies have examined large ethnobotanical texts and clinical-trial data. Some deep-learning algorithms have been used to uncover unfavourable herb-drug interactions, predict bioactivity, and find herb combinations. Text-mining produces high-quality datasets for pharmacological network analysis,

quantitative structure-activity modelling, virtual screening, and other AI applications. NLP and text-mining may bridge computational drug discovery with medical knowledge [16-17].

4.2 Ontologies and Semantic Networks of Herbal Pharmacology.

Ontologies and semantic networks organise and explain complex interactions between herbal ingredients, targets, illnesses, and pharmacological processes. Ontologies reveal hierarchical relationships and shared vocabularies to annotate herbal-pharmacology data from several sources [18-19]. Herb pharmacological ontologies may be linked to active

phytoconstituents, molecular targets, biological pathways, and clinical indications for integrated analysis. This research is further enhanced by semantic networks, which visualise and compute these relations as nodes (entities) and edges (interactions). In advanced research, artificial-intelligence systems may identify novel target-compound-disease correlations, anticipate synergistic interactions, and identify multi-target therapy regimens utilising ontology-based knowledge graphs. Machine-learning methods rank herbal leads using network centrality, similarity, and topological features. Due to its emphasis on reasoning and inference, semantic networks help researchers hypothesise about herb pharmacological effects. Herbal medicine is increasingly using ontologies and semantic networks. AI-based knowledge graphs with TCM and Ayurveda expertise have improved project success. Researchers may use years of medication repurposing data, curated ontologies, semantic links, and AI-based analytics to uncover bioactive molecules and predict harmful interactions. Thus, traditional medicinal knowledge influences basic, evidence-based herbal medicine research.

5. Predictive Modeling and AI-Powered Formulation and Safety Assessment

5.1 AI-Assisted Multi-Target Prediction of Herbal Constituents

The therapeutic effects of herbal medicines are often attributed to the simultaneous interaction of multiple phytoconstituents with diverse molecular targets. Although this multi-target activity may provide advantages in the management of complex and multifactorial diseases, it also complicates the systematic assessment of efficacy, toxicity, and potential off-target effects. AI-based predictive approaches can facilitate the identification and characterization of these complex interactions by integrating phytochemical, protein-target, disease-pathway, pharmacological, and toxicological datasets. Machine Learning (ML) algorithms, including Random Forest (RF), Support Vector Machine (SVM), and artificial neural networks, can analyse large-scale datasets to predict compound–target associations and biological responses. Deep Learning (DL) models can further identify complex nonlinear relationships between phytochemical structures, molecular targets, signalling pathways, and disease phenotypes. Such approaches enable researchers to prioritize compounds with favourable pharmacological profiles while simultaneously identifying potential toxicological liabilities. Network-based AI approaches can construct interconnected networks linking herbs, phytochemicals, molecular targets, metabolic enzymes, transporters, and disease pathways. These models can help characterize synergistic and antagonistic interactions among herbal constituents and identify potential mechanisms underlying both therapeutic and adverse effects.

Importantly, multi-target modelling can also assist in recognizing off-target interactions that may contribute to organ-specific toxicity or clinically relevant adverse reactions. AI-assisted prediction is particularly valuable for complex chronic diseases in which multiple biological pathways contribute to disease progression.

By integrating pharmacological and toxicological information, AI models can support the prioritization of herbal constituents for further experimental validation and reduce unnecessary trial-and-error experimentation. Emerging applications have demonstrated the potential of computational approaches for identifying herbal constituents with anticancer, anti-inflammatory, neuroprotective, and other pharmacological activities while simultaneously improving early-stage safety profiling [20].

5.2 AI-Based Prediction of Synergistic and Antagonistic Effects in Polyherbal Formulations

Polyherbal formulations constitute an important component of Ayurveda, Traditional Chinese Medicine (TCM), and other traditional healthcare systems. Their therapeutic effects may arise from additive, synergistic, or antagonistic interactions among multiple plants and their constituent phytochemicals. However, the large number of possible combinations and the complexity of their molecular interactions make empirical optimization of polyherbal formulations challenging. AI and ML provide promising computational strategies for systematically analysing these multicomponent interactions. By integrating chemical composition, pharmacological activity, toxicological information, omics datasets, and clinical evidence, AI models can predict potential synergistic, additive, or antagonistic effects among herbal constituents. Such predictive frameworks may facilitate the rational selection of plant combinations with enhanced therapeutic efficacy and improved safety profiles. Knowledge graphs and network pharmacology can further represent relationships among medicinal plants, phytochemicals, molecular targets, metabolic pathways, and disease phenotypes. When combined with ML or DL algorithms, these networks can identify highly interconnected components and predict potential interactions within complex herbal formulations. Importantly, the same computational framework can be used to identify combinations that may increase toxicity, alter drug metabolism, or enhance the risk of herb–drug interactions.

AI-assisted formulation modelling may therefore reduce dependence on extensive empirical screening and facilitate the optimization of dose ratios, constituent combinations, and therapeutic targets before experimental evaluation. However, computational predictions should be considered hypothesis-generating rather than definitive evidence of clinical synergy. Experimental validation, standardized phytochemical characterization, pharmacokinetic assessment, and toxicological evaluation remain essential for confirming predicted interactions and establishing the safety and efficacy of polyherbal formulations [21].

5.3 Explainable AI for Herbal Toxicology and Personalized Safety Assessment

Explainable Artificial Intelligence (XAI) represents an important advancement in the application of AI to herbal toxicology because it enables researchers and clinicians to understand the factors underlying model predictions.

Conventional AI and DL models may function as “black boxes,” generating highly accurate predictions without clearly indicating which molecular, biological, or clinical features contributed to the outcome. In safety-critical applications, such limited interpretability can restrict scientific confidence, reproducibility, and regulatory acceptance. XAI approaches can identify and quantify the contribution of individual molecular descriptors, phytochemicals, biological pathways, and patient-related characteristics to a predicted outcome. Common approaches include SHAP (SHapley Additive exPlanations), LIME (Local Interpretable Model-Agnostic Explanations), attention mechanisms, and feature-importance analysis.

These methods can be applied to toxicity prediction, ADMET modelling, herb–drug interaction assessment, and mechanistic toxicology to clarify why a particular herbal constituent is predicted to be safe or potentially hazardous. For example, an AI model may predict a favourable anti-inflammatory profile for curcumin derived from *Curcuma longa*. XAI techniques such as SHAP can identify the molecular descriptors contributing most strongly to the prediction, whereas LIME can provide a local explanation for an individual prediction.

Attention-based models may further highlight molecular features or biological pathways associated with the predicted activity. Similar approaches can be applied to toxicological predictions to identify structural alerts, metabolic liabilities, target interactions, or biological pathways potentially associated with adverse effects. XAI may also contribute to personalized herbal safety assessment by integrating genomic, metabolomic, pharmacokinetic, disease-specific, and clinical information. An interpretable model could help explain why a particular herbal preparation may present a higher risk of toxicity or herb–drug interaction for a specific patient profile. This capability may support individualized risk stratification and more informed therapeutic decisions. Nevertheless, explainability should not be equated with causality or clinical validity. AI-generated explanations require independent experimental and clinical validation before being used to support regulatory or therapeutic decisions. Integrating XAI with standardized toxicological datasets, mechanistic studies, and prospective validation could improve transparency, reproducibility, and responsible implementation of AI in herbal safety assessment [22–23].

6. AI-Driven Prediction of Herb–Drug Interactions, Toxicity, and Safety Assessment

6.1 AI-Based Prediction of Adverse Effects, Contraindications, and Organ-Specific Toxicity

Herbal medicines may produce adverse effects or contraindications because of intrinsic toxicity, contamination, dose-related effects, metabolic variability, or interactions with other medicines. Conventional toxicity assessment relies substantially on experimental studies and clinical observation, which can be time-consuming and may identify safety signals relatively late. AI and machine-learning models can use chemical structures, molecular descriptors, experimental toxicology data, pharmacokinetic parameters, and clinical

observations to support earlier toxicity prediction. These models can estimate risks such as hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, genotoxicity, reproductive toxicity, and cytotoxicity and can identify structural alerts or toxicophoric patterns associated with adverse outcomes. Integration of multi-omics and patient-related data may further help identify biological pathways and susceptibility factors linked to herb-induced toxicity. AI therefore provides an opportunity to shift herbal safety assessment from reactive identification of adverse effects toward proactive, predictive toxicology, while model predictions must remain subject to appropriate experimental and clinical validation [24–25].

6.2 AI-Based Modelling of Herb–Drug Interactions with Conventional Drugs

Herbs may alter drug-metabolizing enzymes, transporters, receptors, and signalling pathways, creating clinically relevant herb–drug interactions (HDIs), particularly in patients receiving multiple medicines. AI-based interaction modelling can integrate information on phytochemicals, conventional drugs, target proteins, cytochrome P450 enzymes, P-glycoprotein and other transporters, metabolic pathways, and reported clinical outcomes. Machine learning, network pharmacology, and knowledge graphs can be used to identify potential synergistic, antagonistic, or adverse interactions and to estimate interaction severity. Deep-learning approaches may also model nonlinear interactions arising from complex multi-component herbal preparations. Such systems can support early identification of contraindications and potential pharmacokinetic or pharmacodynamic interactions, but predicted HDIs require experimental, pharmacokinetic, and clinical confirmation before being translated into dosing or regulatory recommendations [26–27].

6.1.2 AI-Assisted Prediction of Toxicological Mechanisms and Molecular Pathways

AI-assisted toxicology can move beyond endpoint prediction by helping connect chemical exposure with molecular initiating events, key biological pathways, and adverse outcome pathways. Integration of transcriptomics, proteomics, metabolomics, and pathway-level information can reveal changes associated with oxidative stress, mitochondrial dysfunction, inflammation, apoptosis, endocrine disruption, and other toxicological processes. Network-based models can link phytochemicals to molecular targets, enzymes, signalling pathways, and organ-level outcomes, providing a mechanistic context for predicted toxicity. This approach is particularly relevant to herbal preparations because several constituents may act on overlapping biological pathways and may modify one another's exposure or toxicity. Mechanistic AI models can therefore assist in identifying candidate toxicants, generating testable hypotheses, and prioritizing targeted in vitro or in vivo experiments. Importantly, computationally predicted mechanisms should be regarded as hypotheses requiring experimental confirmation rather than as definitive evidence of toxicity [24–27].

Several AI-driven databases and computational tools can support herbal drug research and toxicological assessment. DeepChem provides machine-learning capabilities for molecular modelling, QSAR prediction, and virtual screening, while transformer-based models such as MolBERT can support prediction of molecular properties, bioactivity, and ADMET characteristics. PharmMapper uses pharmacophore mapping and reverse screening to predict potential targets, and HerbalDB integrates pharmacological, phytochemical, and ethnobotanical information. When linked with validated toxicological datasets, such platforms can also assist in screening structural liabilities, predicting toxicity-related endpoints, and prioritizing compounds for safety testing. Their value in herbal toxicology depends on dataset quality, appropriate endpoint definition, external validation, and transparent reporting of model performance.

An integrated safety framework can combine toxicity prediction, ADMET profiling, HDI prediction, and mechanistic toxicology into a single decision-support workflow. Chemical structure and phytochemical composition can first be evaluated using QSAR and structural-alert models, followed by prediction of absorption, distribution, metabolism, transport, and elimination characteristics. Potential organ-specific toxicity and HDIs can then be estimated using toxicological, pharmacological, and clinical datasets. Knowledge graphs and multi-omics models can provide mechanistic interpretation, while explainable AI can identify the molecular or biological features contributing to a risk prediction. Such a workflow can classify herbal candidates into lower- and higher-priority groups for experimental evaluation, thereby improving the efficiency of preclinical safety assessment. The framework should be used as a complementary tool alongside standardized analytical characterization, validated in vitro assays, animal studies where scientifically justified, and clinical evidence.

AI-integrated natural-product platforms can combine network pharmacology, machine learning, deep learning, and molecular modelling to support both therapeutic discovery and safety evaluation. Multi-component systems can be examined for target interactions, pharmacokinetic properties, and potential toxicity, while graph-based approaches may identify patterns of synergistic or antagonistic interactions. Integrating patient-specific or omics information with natural-product databases may further support individualized prediction of therapeutic response and adverse-event susceptibility. These platforms therefore have potential to connect natural-product discovery with predictive toxicology and safety-oriented candidate prioritization, provided that computational findings are confirmed using appropriate experimental evidence.

AI can support risk stratification by integrating predicted exposure, pharmacokinetic behaviour, toxicity endpoints, interaction potential, and mechanistic evidence. A safety-oriented model may assign confidence or risk categories to phytochemicals and herbal formulations, helping researchers prioritize compounds for confirmatory testing. When uncertainty estimates and model explanations are available,

they can also indicate which data gaps most strongly influence the predicted risk. This is especially important for herbal products with variable composition, because differences in plant species, geographical origin, extraction procedures, and constituent concentrations can alter both efficacy and safety. Consequently, AI-based risk scores should be interpreted in the context of product standardization and the quality of the underlying toxicological dataset.

AI-driven herbal research is advancing rapidly, yet toxicological dataset curation and model validation remain major challenges. Herbal databases may differ in plant identity, extraction procedures, constituent concentrations, exposure levels, experimental systems, and definitions of adverse outcomes. Such heterogeneity can introduce bias and reduce the generalizability of toxicity and ADMET models. Robust safety prediction requires standardized chemical characterization, harmonized toxicological endpoints, appropriate negative and positive controls, representative training datasets, external validation, uncertainty assessment, and prospective experimental testing. Explainability is also important because researchers and regulators need to understand why a model classifies a phytochemical or herbal formulation as potentially hazardous. FAIR data practices and transparent reporting can strengthen reproducibility and support responsible adoption of AI in herbal toxicology [31].

7.1 Tools and Databases: DeepChem, MolBERT, PharmMapper, HerbalDB

Several artificial intelligence-driven databases and computational tools have been created to aide in the identification of herbal treatment. The open-source library DeepChem is one such resource and offers strong predictive performance of multi-target bioactive compounds, enables high-throughput molecular modelling, QSAR prediction, and virtual natural product screening [28]. By learning molecular representations and predicting attributes, transformer-based deep-learning model MolBERT may enhance phytochemical bioactivity and ADMET predictions. Pharm Mapper, based on pharmacophore mapping and reverse screening, combines chemical information with herbal component therapeutic indications to predict potential targets. Pharmacological, phytochemical, and ethnobotanical data in HerbalDB makes it helpful for AI-based mining and formulations. These databases together may discover computationally identical drug candidates to experimental leads. These systems can examine multicomponent extracts and polysaccharides since they are scalable and integrative. Structural, chemical, and biological data enable researchers to mimic screening, project target engagement, and assess toxicity in a fraction of the time utilising standard methods. These databases are augmented with AI methods to estimate expected medicinal efficacy, network pharmacology profiles, and pattern recognition, allowing rational herbal product design. These technologies make herbal medicine more organised, evidence-based, and reproducible.

The success of these platforms has led to community-supplied repositories where scientists may exchange datasets, validated models, and methods. In herbal drug discovery collaborations, AI will improve data quality, inventiveness, and model robustness. All platforms provide a consistent basis for future herb research by combining the latest AI advancements with ethnobotany history.

AI-enhanced herbal products present distinctive regulatory challenges because herbal preparations are often multi-component and computational models may generate probabilistic predictions rather than direct evidence of safety. Regulatory assessment requires reliable characterization of the herbal material, reproducible analytical methods, validated toxicological evidence, and transparent documentation of model development and performance. AI-derived predictions of ADMET behaviour, toxicity, and herb–drug interactions should therefore be treated as supportive evidence and integrated with experimentally generated safety data. Standardized reporting of datasets, model architecture, validation procedures, uncertainty, applicability domain, and external performance will be important for regulatory confidence. Collaboration among regulators, computational scientists, toxicologists, pharmacognosists, and pharmacologists is needed to establish fit-for-purpose frameworks for AI-assisted herbal safety assessment [32]. Transparency and explainability are particularly important when AI models are used for toxicological decision-making. Opaque deep-learning models may provide accurate predictions without clearly identifying the chemical or biological factors responsible for a safety classification. Explainable AI approaches such as SHAP, LIME, attention mechanisms, and feature-importance analysis can identify influential molecular descriptors, phytochemical features, biological pathways, or exposure-related variables. Such explanations can help researchers evaluate biological plausibility, design confirmatory experiments, identify potential data artefacts, and communicate model outputs to regulators and clinicians [29-30]. Explainability should therefore be considered an important component of responsible AI-assisted toxicity prediction, alongside quantitative validation and uncertainty assessment [33].

AI-driven herbal research is advancing rapidly, yet model validation and dataset curation remain issues. Herbal databases are inconsistent owing to ethnobotanical reporting, extraction processes, and plant materials. These disparities may bias AI models, reducing predicted accuracy and generalisability. Therefore, it is vital to standardise datasets with exact pharmacological, biological, and chemical annotation for model training.

Validating accurate models is the biggest challenge. Most AI models are trained and evaluated on short or manually picked datasets, which increases overfitting and poor generalisation. Testing models on many datasets, external validation, and experiment feedback are needed to create accurate predictions. To ensure regulatory and clinical adoption of AI models, explainability and interpretability are crucial.

Other ethical and legal issues arise. Trust in AI-powered herbal medicine discovery is needed for credibility, openness, and FAIR (Findable, Accessible, Interoperable, Reusable) compliance. Community movement, formalisation of methods, and experimental testing to corroborate AI-based projections may overcome such issues [31].

8. Regulatory, Validation, Explainability, and Safety Considerations for AI-Assisted Herbal Research.

8.1 Challenges in Regulatory Approval of AI-Assisted Herbal Drugs

AI-enhanced herbal drugs have some specific difficulties in terms of validation, because of multi-component character of herbal preparations, and computational procedures used to assess them. There are generally strict rules that drug regulators need unambiguous safety, efficacy and reproducibility, but AI-based predictions on multi-target phytocompounds blur conventional evaluation models. These challenges are compounded by the fact that different geographic regions use different herbal materials, and standardised methods of testing and validating AI models are lacking. To protect patient safety, as well as to enable the clinical use of AI-guided herbal treatments, standardisation of regulatory requirements is necessary. There are small existing standard frameworks in the case of herbs products, despite the fact that companies like FDA and EMA have started to provide guidelines on the use of AI in developing drugs. Regulatory clearance of AI-derived ADMET, multi-target pharmacology and herb-drug interaction prediction requires a strong experimental support. Standardised reporting and careful documentation are also necessary to meet the scrutiny of the regulators due to problems of reproducibility, model interpretability and data quality. The solution of these challenges will involve the work of regulators, computational scientists and ethnopharmacologists [32]. The integration of AI with genomics, proteomics, metabolomics, systems biology, and network pharmacology can provide a more comprehensive view of the mechanisms underlying both therapeutic effects and toxicological responses to herbal medicines. Compound–target–pathway networks can be used to identify potential molecular initiating events, toxicity-associated pathways, and multi-component interactions. Multi-omics models may also help identify biomarkers of susceptibility, exposure, or organ injury and support more individualized safety assessment. Combining ethnophar

macological knowledge with standardized chemical and toxicological data could improve prediction of efficacy and adverse outcomes while reducing uncertainty in complex herbal preparations [35].

Herbal drug discovery is under the condition of transparency and explainability, which are prerequisites of AI-facilitated discovery. The lack of interpretability in deep neural networks and other opaque AI models makes the model outputs not relatable by the regulators and clinicians. Respondent to explainable AI (XAI) methods, attention mechanisms, SHAP

(SHapley Additive exPlanations), and LIME (Local Interpretable Model-Agnostic Explanations) are methods to identify critical phytochemical properties and visualise model reasoning. By interpretability, AI predictions can be supported by a scientific justification and can be compared to known pharmacological backgrounds. In addition, explainable models can be used to establish the safety and effectiveness of herbal preparations, which is required of multi-component extracts whose bioactivity profiles are necessarily complex [33]. Transparency leads to reproducibility, compliance with regulations, and critical acceptance of clinical practice by closing the gap between prediction and actual therapeutic practice. By incorporating XAI and using ethnopharmacological data, one has the potential to detect silent compound-target-disease interactions and maintain accountability and adhere to high ethical standards.

Digital twins and AI-based virtual patient models may provide future tools for exploring exposure, pharmacokinetic behaviour, therapeutic response, and potential adverse effects of herbal medicines before clinical investigation. By integrating patient-specific physiology, biomarkers, medication history, and omics information, such models could simulate different dosing scenarios and identify individuals who may be at increased risk of toxicity or herb–drug interactions. For complex polyherbal formulations, digital simulations may help prioritize combinations and experimental conditions. However, these systems require high-quality clinical and toxicological data and rigorous prospective validation before they can be used for regulatory or clinical safety decisions [34–36].

A future direction in herbal pharmacology is the development of increasingly autonomous AI systems that can screen phytochemicals, predict pharmacological activity, evaluate ADMET properties, identify toxicity liabilities, model herb–drug interactions, and optimize formulations. Safety should be embedded throughout this pipeline rather than evaluated only after therapeutic candidates have been selected. Self-learning systems may incorporate laboratory findings, clinical observations, and toxicovigilance data to refine predictions, identify knowledge gaps, and recommend targeted experiments. Nevertheless, autonomous decision-making in toxicology must remain subject to human oversight, validated workflows, explainability, ethical governance, and regulatory controls to ensure that computational efficiency does not replace scientifically necessary safety evaluation [37].

9.1 Integration with Multi-Omics, Systems Toxicology, and Network Pharmacology

The integration of artificial intelligence with herbal pharmacology provides a promising framework for more systematic, predictive, and safety-oriented herbal drug development. AI-assisted QSAR modelling, virtual screening, ADMET prediction, toxicity assessment, herb–drug interaction modelling, network pharmacology, and multi-omics analysis can help identify therapeutic opportunities while simultaneously revealing potential safety liabilities.

This is particularly important for herbal medicines because their multi-component composition can produce complex pharmacological and toxicological effects. AI can support proactive identification of hepatotoxic, cardiotoxic, nephrotoxic, neurotoxic, genotoxic, cytotoxic, and interaction-related risks and can help connect predicted adverse outcomes with underlying molecular pathways. However, AI predictions should not be interpreted as substitutes for validated toxicological experiments or clinical evidence. Dataset heterogeneity, limited external validation, model uncertainty, lack of interpretability, product variability, and evolving regulatory expectations remain significant challenges. Future progress will require standardized toxicological datasets, transparent and explainable models, uncertainty-aware prediction, multi-omics integration, rigorous experimental validation, and responsible data governance. A safety-centred AI framework can ultimately strengthen the translation of traditional medicinal knowledge into reproducible, evidence-based, and safer herbal therapeutics.

9.2 Digital Twins and AI Avatars for Predictive Herbal Safety Assessment

Digital twin's virtual patient replicas represent the first chance in history to test herbal medicines in silico, reducing the risk linked to test them in reality, but forecast their interactions, side effects, and efficacy. Patient-specific pharmacology and physiology Digital twins can predict the outcomes of herbal extracts, eliminating the necessity to perform experiments in vivo. Multi-compound herbal preparations can also be modelled by AI avatars, which simplifies the optimisation of therapeutic regimens and dosage combinations. They are virtual platforms that act as areas of convergence between predictive algorithms and clinical expertise allowing real-time monitoring of patients, adaptive learning, and protocol design. These kinds of simulations are very useful especially in the case of a complex polyherbal formulation and they are very safe, cheaper to conduct experimental work, and can fasten the process of translational research [36].

9.3 Towards Autonomous, Safety-Centred AI Systems for Herbal Drug Development

A new move in herbal pharmacology aims at developing independent drug-discovery facilities that can identify, optimize and validate new herbal leads right through to clinical validation. The sites minimize human intervention by taking advantage of AI-based screening of compounds, QSAR modeling, network pharmacology, prediction of toxicity, and formulation design, which guarantee efficiency and reproducibility. Self-learning systems constantly absorb knowledge of clinical trials, laboratory reports, and ethnopharmacological sources to perform refining of predictive models and suggest a new combination of drugs. The method has the potential to reveal the bioactive molecules that were not accessible earlier in complex herb analogues, thereby reducing the developmental cycles and minimizing expenses. However, the introduction of explainable AI, legal

adherence, and strict ethical supervision are essential to guarantee the safe and responsible usage [37].

Discussion and Conclusion

The meeting point between artificial intelligence and herbal pharmacology is uncovering a new aspect of discovering and developing medicinal agents. Through the combination of network pharmacology, computational modelling, and multi-omics information AI assists in systematic studies of multi-component herbal preparations. This interaction clarifies bioactive compounds, establishes synergistic interactions and directs accurate treatment protocols. AI-enhanced QSAR/ADMET predictions, virtual screening, predictive modelling, and in silico assays find their place in the discovery pipeline and reduce the need to use empirical methods and minimise lead optimisation times. The use of AI also promotes patient-specific digital twins, simulation-based clinical trials, and adaptive formulation design, which will serve to provide accuracy in herbal medicine. However, there are still a lot of challenges. The standardisation of validation procedures, the ethical treatment of ancient knowledge, model interpretability and regulatory approval procedures are still formidable challenges. To solve these problems, explainable AI systems, strict experimental validation, and fair data stewardship should be adopted, so that the computational predictions may be cautiously transferred to effective and socially responsible herbal therapeutics. The combination of ancient knowledge and state-of-the-art technology, AI-based solutions will bring a revolution in the field of herbal drug discovery, which will eventually result in reproducible, high-throughput, and precisely targeted therapeutic solutions to more and more complicated diseases.

ACKNOWLEDGEMENTS

The authors are grateful to Harcourt Butler Technical University and Maharana Pratap College of Pharmacy and Pharmaceutical Sciences Kanpur, Uttar Pradesh, India for Technical and Administrative Support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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How to cite this article:

Mishra R, Kumari M, Kumar A, Gupta G, Biswal LP, Dubey A. Artificial intelligence in herbal toxicology: ai-assisted toxicity prediction, admet assessment, herb–drug interactions, and safety evaluation. *International Journal of Pharmaceutical Science and Medicine* 2026; 4(1): 23-35