Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 15 March 2026
Revised 25 April 2026
Accepted 12 May 2026

Natural Resources for Human Health 2026, Vol. 6 (3): 283–294

KEYWORDS:
Medicinal plants; Artificial intelligence; Machine learning; Drug discovery; Molecular docking; Network pharmacology; Natural products.

Medicinal Plant Research: Current Advances, Challenges, and Future Directions

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ABSTRACT: Medicinal plants have been integral to the health care systems for centuries and are still a valuable source of bioactive compounds for developing new therapies. Although medicinal plants have a great potential in the field of medicine, the conventional approach of medicinal plant research is constrained by time consuming phytochemical isolation, lengthy experimental validation and high attrition during the drug development process. Thanks to recent developments in computing technology, this picture has changed to allow for the fast identification, characterization and optimization of potentially therapeutic phytochemicals. In this context, the application of AI, machine learning, CADD, molecular docking, molecular dynamics (MD) simulations, quantitative structure–activity relationship (QSAR) modeling, network pharmacology, multi-omics integration, and ADMET prediction has been shown to speed up the process of natural product-based drug discovery and decrease both drug development costs and timelines. Besides, the virtual screening and target identification through large-scale databases have been made possible by publicly available chemical and pharmacological databases, thereby enabling the discovery of complex mechanisms of herbal medicines. The integration of new technologies like deep learning, generative AI, and explainable AI is also further developing computational medicinal plant research, which is increasingly improving the precision of predictive models and the interpretability of the AI model. However, several obstacles such as the scarcity of good quality datasets, inconsistencies in the

phytochemical databases, poor experimental validation, concerns over algorithm transparency, and many other challenges remain and hinder the wide adoption of these tools. It provides an overview of the latest development of computational platforms used for research on medicinal plants, their use and limitations, some representative examples of medicinal plant research applying computational approaches and what is needed for the integration of computational technologies with experimental pharmacology. Together, these computational strategies are revolutionizing medicinal plant research and speeding up the identification of plant-based therapies with improved safety, efficacy and economical viability.

1. INTRODUCTION

Medicinal plants are one of the oldest and most consistent sources of therapeutic agents, and have been the basis of traditional healthcare systems for thousands of years, across a wide range of cultures. The natural products from plants have remained important in today's synthetic drug era because of their excellent diversity of structure, biological specificity, and wide range of pharmacological activities. The use of medicinal plants for drug production has been important throughout human history, with many drugs used to treat cancer, infectious diseases, malaria and cardiovascular illnesses being derived directly and indirectly from nature (1,2). Natural products have distinct chemical scaffolds and stereochemical complexity which are different from synthetic chemical libraries and hence are useful starting points for discovery of new therapeutic agents. Alkaloids, flavonoids, terpenoids, phenolic compounds, glycosides and saponins are phytochemicals with various cancer, diabetes mellitus, cardiovascular disorders, neurodegenerative disorders, inflammatory disorders and infectious diseases-related biological activities. They can interact with several molecular targets, thus triggering a renewed interest in the potential use of medicinal plants for multitarget drug discovery and precision therapeutics (1–3). The field of medicinal plant research has been revolutionized by the recent development of computational sciences which allow a rapid, cost-effective and high throughput investigation of phytochemicals. The incorporation of artificial intelligence (AI), machine learning (ML), computer-aided drug design (CADD), molecular docking, molecular dynamics (MD) simulations, quantitative structure–activity relationship (QSAR) modeling, network pharmacology, and multi-omics technologies has vastly facilitated all aspects of natural product-based drug discovery. These computational methods enable virtual screening of thousands of phytochemicals, prediction of their biological activity, identification of therapeutic targets, determination of their pharmacokinetic properties, and ranking of potential lead compounds prior to experimental testing or validation, which greatly lowers the cost and time of the drug development process (4–6). Of these, Artificial Intelligence has proven to be one of the biggest advancements in pharmaceutical research. Machine learning models have the ability to analyze large amounts of data from various experiments like chemical, genomic, transcriptomic, proteomic, and pharmacological datasets in order to identify new relationships or patterns between phytochemicals and disease-associated targets in an efficient manner. Machine learning models have also shown to be very powerful in predicting bioactivity, toxicity, molecular properties and drug-target interactions, and enhancing lead optimization and compound prioritization. Additionally, deep learning architectures and generative AI models are being increasingly used to create novel molecules with new therapeutic activities and physiochemical properties that are inspired by natural products (4–6). The use of computer-aided drug design has also boosted the research of medicinal plants by offering reliable in silico tools for analyzing the interactions between phytochemicals and biological targets. While molecular docking can be used for predicting the preferred binding orientation and affinity of the ligands toward their target proteins, molecular dynamics simulations can be used for evaluating the conformational stability and dynamic behavior of protein–ligand complexes under physiological conditions. Rational lead optimization can be achieved by correlating the structural features with the biological activity, using complementary approaches such as QSAR modeling and pharmacophore analysis, which helps to avoid the need of comprehensive laboratory screening (4,7). The massive growth of publicly available databases of chemicals and drugs has further improved computational medicinal plant research. The information on the structures of phytochemicals, biological activities, molecular targets, pharmacokinetics and toxicity profiles is complete in various resources such as PubChem, ChEMBL, DrugBank, NPASS, IMPPAT, BindingDB, and SwissADME. The building of these repositories into AI-supported computational platforms has made an integrated digital platform that has the potential to speed up virtual screening, target discovery and lead optimization and enhance the reproducibility and accessibility of the data for multi-disciplinary research

groups (5,8). Their computational platforms have revolutionized medicinal plant research, but there are a number of issues that need to be resolved. There are still a number of challenges on the way to clinical translation, such as limited availability of standardized datasets of phytochemicals, inconsistencies in experimental validation, algorithmic bias, limited interpretability of models and poor integration of computational prediction and laboratory studies. Future research should aim to develop robust, reliable, transparent, and reproducible computational pipelines for medicinal plant-based drug discovery through the integration of explainable artificial intelligence, the quality of available multi-omics datasets, the integration of cloud computing, and experimental pharmacology (1,4,8). The present review describes the recent computational platforms that are revolutionizing the research on medicinal plants and natural product-based drug discovery. It thoroughly reviews recent developments in artificial intelligence, machine learning, computer-aided drug design, molecular simulations, network pharmacology, systems biology and digital databases, and underscores their current applications, limitations and future directions. These technologies, which combine computation intelligence and traditional pharmacognosy, are expected to speed up the development of safer, more effective and scientifically validated plant-based therapeutics for the management of complex human diseases.

2. EVOLUTION OF COMPUTATIONAL APPROACHES IN MEDICINAL PLANT RESEARCH

The use of computational technologies in medicinal plant research has gone from simple database searching to more advanced platforms that are now powered by artificial intelligence (AI), enabling them to predict biological activity, seek out therapeutic targets or optimize lead compounds. The initial computational studies focused on a variety of chemical databases, molecular descriptors, and statistical models to assess phytochemical properties and to establish preliminary stucture–activity relationships. These methods increased the efficiency of natural product research but were still limited by the computational power available, the lack of data integration and the relatively low complexity of the predictive algorithms (9,10). Cheminformatics, Bioinformatics and High-Performance Computing have developed at a fast pace over the last 20 years and have made medicinal plant research into a data-based science. These large libraries of information in the form of phytochemical structures, protein sequences, biological pathways, and pharmacological data have allowed scientists to screen thousands of natural compounds virtually down to a fraction of the time that it would normally take to screen them in the laboratory. This shift has led to a considerable decrease in the cost and time of early stage drug discovery as well as enhancement of the discovery of bioactive phytochemicals that are promising drugs (9-11). Computational chemistry, coupled with systems biology, has further extended the scope of medicinal plant research. Researchers no longer study a single compound or single protein targets; they now study complex interactions between the phytochemicals, genes, proteins, signaling pathways and disease networks. This systems-level approach is especially relevant because the herbs typically have several bioactive components with several molecular targets that work synergistically. Hence, computational methods have emerged as essential tools for the comprehension of the pharmacological complexity of medicinal plants and elucidation of their mechanisms of action (10–12).

Table 1. Major computational platforms used in medicinal plant research

Platform	Application	Outcome
Artificial Intelligence (AI)	Bioactivity prediction	Lead identification
Machine Learning (ML)	Compound screening	Target prediction
Molecular Docking	Protein–ligand interaction	Binding affinity
Molecular Dynamics	Complex stability	Interaction validation
QSAR	Activity prediction	Lead optimization
Network Pharmacology	Multi-target analysis	Mechanism elucidation
Multi-Omics	Biomarker discovery	Pathway analysis
ADMET Prediction	Safety assessment	Candidate prioritization

In recent years, AI and machine learning have become pivotal innovations in the field of natural product drug discovery. The approaches can effectively handle large number of multidimensional data obtained from genomics, transcriptomics, proteomics, metabolomics and chemical analysis and extract the relationship that is not easy to capture in the conventional statistical analysis. Machine learning algorithms have shown to be efficient in predicting various biological activities, drug–target interactions,

toxicity, kinetic properties, and molecular similarity which aids in prioritizing lead compounds for experimental validation of the chemical lead to biological lead (11,12). In addition to AI, structure-based computational approaches have also seen significant improvements. Molecular docking has now become a regular method to analyse the protein–ligand binding and molecular dynamics simulations offer dynamic information about the stability and conformational changes of the ligand–protein complex in the physiological conditions. Such strategies allow scientists to study binding mechanisms in a more detailed way prior to carrying out expensive lab experiments. Besides, with the development of quantitative structure–activity relationship (QSAR) modeling, pharmacophore mapping, and virtual screening, the identification and optimization of medicinal plant-derived compounds have become much more efficient (9–12). In more recent times, computational medicinal plant research has started to take a new turn that incorporates deep learning, generative AI, cloud computing technologies, explainable AI, and digital twin approaches. These platforms not only enhance the predictive power, but also enable automated hypothesis generation, molecular design, and personalized phytomedicine development. Computational predictions are increasingly being validated by experimentation, thus allowing establishment of robust and repeatable pipelines that can facilitate the shift of medicinal plant derived compounds into clinically useful therapeutics (10–12). A history of the development of computational methods used in medicinal plant research is shown in Figure 1 and the present major computational environments used in phytopharmaceutical drug discovery are laid out in Table 1 (9–12).

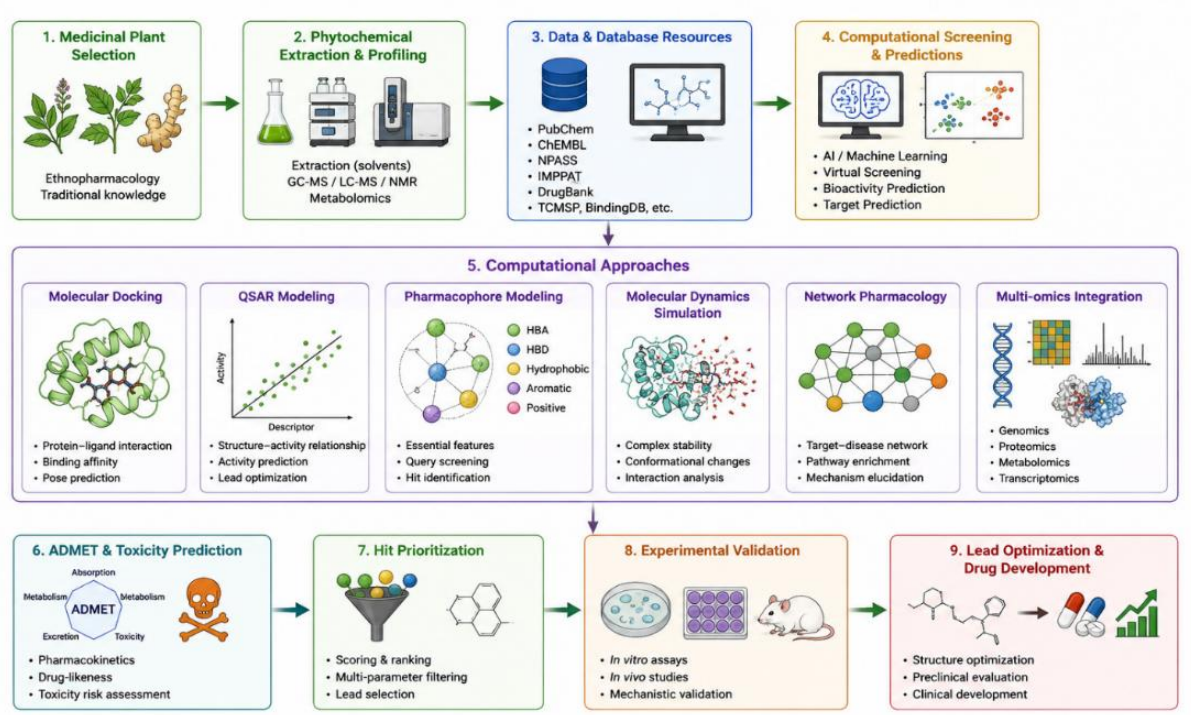

Figure 1. Integrated computational platforms accelerating medicinal plant-based drug discovery

3. MAJOR COMPUTATIONAL PLATFORMS FOR MEDICINAL PLANT DRUG DISCOVERY

3.1 Artificial Intelligence and Machine Learning

In recent years, artificial intelligence (AI) and machine learning (ML) have become game-changers in the domain of computational technologies that are transforming medicinal plant research and natural product-based drug discovery. The key difference lies in how AI handles the large volume of data, which is multidimensional and often too intricate to be recognized using traditional algorithms and human interpretation.Unlike traditional computational methods, which are based on pre-defined algorithms and manual interpretation, AI uses data-driven learning to identify complex patterns in multidimensional and large datasets. These capabilities allow bioactive phytochemicals to be identified rapidly, molecular targets predicted, lead compounds optimised, and pharmacological properties assessed much more efficiently than conventional experimental

approaches (13,14). With the advent of several databases of phytochemicals, high throughput screening data, genome information, and pharmacologic repositories, AI has gained increasing traction in the field of medicinal plant research. Machine learning algorithms can also process thousands of natural compounds, and correlate their structural features with biological activities, enabling the discovery of new therapeutic targets. Random Forest (RF), Support Vector Machine (SVM), Extreme Gradient Boosting (XGBoost) and Artificial Neural Networks (ANNs) are commonly used supervised learning models for bioactivity prediction, phytochemical classification and drug target prediction. The unsupervised learning techniques like clustering algorithms and principal component analysis are used to search for hidden relationships between phytochemicals, and categorize medicinal plants according to their chemical composition (13, 14). One of the major benefits of AI is that it can optimize virtual screening processes. Traditional high throughput screening may need a lot of laboratory resources and financial investments. By using AI-assisted virtual screening, researchers can prioritize compounds for biological activity even before they undergo experimental testing to cut down on the number of compounds they have to test in the lab. This approach significantly reduces the amount of time spent on the early stages of drug discovery and boosts the chances of discovering promising lead molecules in complex medicinal plant extracts (13,15). Another area where machine learning has proven to be valuable is in predicting drug–target interactions. Combining chemical properties, molecular fingerprints, protein sequences, and biological activity information allows ML models to accurately predict possible interactions between phytochemicals and disease-related proteins. These predictions help to identify new therapeutic targets and can guide the selection of promising compounds for more computational and experimental studies (14,16). More recently, a specialized type of machine learning known as deep learning has also improved the prediction performance, using multi-layered neural networks that can learn complex nonlinear relationships. The molecular property prediction, estimation of toxicity, protein-ligand interaction analysis, and molecular representation learning are the areas where convolutional neural networks (CNNs), recurrent neural networks (RNNs), and graph neural networks (GNNs) have proven to be very successful. Such sophisticated architectures can identify useful features directly from the molecular structure, without manual feature engineering, which not only enhance prediction accuracy, but also mitigate analytical bias (15–17). There has been significant progress in the field of generative AI in recent times, which has opened up new avenues for medicinal plant-based drug discovery. These generative models can be used to generate novel molecules with retained desirable pharmacological properties, enhanced drug-likeness, selectivity, and pharmacokinetic properties. These methods have opened up a large scope of chemical space for optimization of natural products, and they have helped to develop a series of semi-synthetic compounds based on natural products metabolites from plants (16,17). Despite these progressions, there are still a few obstacles that hinder the broad use of AI in medicinal plant research.Although these advancements have been made, there are still a number of challenges that need to be overcome in order to fully utilize AI in the study of medicinal plants. The effectiveness of predicting the performance of machine learning models is heavily reliant on the quality, diversity, and standardization of training data. The availability of many of the phytochemical databases is incomplete and some of them have inconsistent biological annotations, resulting in low model generalizability. Furthermore, the transparency, interpretability and reproducibility of the algorithm are still very important, especially for deep learning approaches that are frequently perceived as "black-box" algorithms. Explainable AI (XAI), benchmark datasets and interdisciplinary collaboration between computational scientists and pharmacologists are anticipated to overcome these shortcomings and promote confidence in the use of AI for phytopharmaceutical discovery (13–17). In Table 1, the most important AI and machine learning approaches applied in medicinal plant research and their main applications are summarized. In addition, the use of these techniques in the computational drug discovery pipeline is depicted in Figure 1 (17).

3.2 Computer-Aided Drug Design (CADD)

The use of computer-aided drug design (CADD) has emerged as an essential tool in the research of medicinal plants, offering drug design-related computational strategies for identification, evaluation and optimisation of bioactive phytochemicals. CADD combines aspects of computational chemistry, structural biology, cheminformatics and molecular modeling to foresee interactions between natural products and biological targets prior to lab tests. Conventional drug discovery processes are expensive, require a significant amount of experimental work, and can take a long time to find a promising lead compound in complex phytochemical libraries. CADD can significantly decrease the time, expense, and experimental burden associated with these conventional processes. CADD can be mainly classified into two types, namely structure-based drug design (SBDD) and ligand based drug design (LBDD). Structure-based methods involve the three-dimensional structure of the target protein, which can be determined using X-ray crystallography, nuclear magnetic resonance (NMR), cryo-electron microscopy (cryo-EM), or computational prediction methods like the AlphaFold protein structure prediction software, to assess the binding affinity and

interaction patterns of phytochemicals. Ligand based approach on the other hand is based on the structure and biological properties of known active compounds to find new molecules with similar pharmacological properties. Both strategies have been utilized in the drug discovery of medicinal plants, especially with the support of AI driven predictive models (18–20). Virtual screening is one of the major uses of CADD in medicinal plant research that allows thousands of phytochemicals to be screened rapidly against a selected therapeutic target. Virtual screening uses molecular descriptors, docking scores, and pharmacophore features to prioritize compounds that have the highest binding affinity and are drug-like. This computational filtering greatly decreases the number of candidates that need to be validated in experiments and enhances the efficiency of the identification of leads. Many studies have been able to use virtual screening techniques to identify inhibitors of enzymes and receptors related to cancer, diabetes, viral infections, and neurodegenerative diseases from plants (18,20). Lead optimization is still another important application of CADD. Once the active phytochemicals are identified, computational approaches are used to either modify the molecular structure to make it more potent, more selective, more easily absorbed into the body, and/or safer. The use of molecular descriptors, energy minimization and predictive algorithms help researchers assess the impact that structural modifications will have before embarking on the synthesis of the molecule, saving time and money in traditional medicinal chemistry. This optimization process is iterative and it has become more and more crucial to convert naturally occurring compounds into clinically viable drug candidates (19,20). The use of CADD along with AI, machine learning, molecular docking, molecular dynamics simulation, and the prediction of ADMET has enhanced the medicinal plant based drug discovery in a great way. These complementary computational platforms offer a complete environment to search for new therapeutic targets, assess molecular interactions, predict pharmacological activity and rank lead compounds for experimental testing. Hence, today, the CADD has become an important tool in the field of computational phytopharmacology and is still contributing to the translation of the compounds derived from medicinal plants into potential therapeutic agents (18–20).

3.3 Molecular Docking and Molecular Dynamics Simulation

In medicinal plant research, the molecular docking and molecular dynamics (MD) simulation are two of the most popular computational methods for analyzing the interaction between phytochemicals and disease-related biomolecular targets. These techniques are integral to structure-based drug design and can offer a wealth of information about the binding properties, stability, and mechanisms of action of natural products before they are tested in the laboratory. They have been instrumental in bringing the field of phytopharmaceutical research to the forefront and have contributed significantly to the speed of lead identification and overall decrease in the time and costs of conventional drug discovery (21,22). In molecular docking, the preferred binding orientation of a phytochemical in the active site of a target protein and its binding affinity are predicted by the use of scoring functions. This method allows for the fast virtual screening of large phytochemical collection of compounds and can be used against therapeutic targets involved in cancer, diabetes, infective diseases, cardiovascular diseases, or neurodegenerative diseases. Besides identifying potential lead compounds, the docking analysis also provides information regarding the important molecular interactions involving hydrogen bonding, hydrophobic interaction, electrostatic interaction, and π–π stacking that play a key role in ligand binding and biological activity (21). While molecular docking gives a snapshot of protein–ligand interactions, biological systems are dynamic. However the limitation of Molecular dynamics simulation is to predict the conformational flexibility and temporal stability of protein–ligand complexes under simulated physiological conditions. Root mean square deviation (RMSD), hydrogen bond occupancy, root mean square fluctuation (RMSF), radius of gyration (Rg) and binding free energy are among the commonly used parameters for evaluating stability and reliability of docked complexes. Such simulations increase the confidence in the computational predictions and allow selection of promising phytochemicals to be tested in the laboratory (22,23). Molecular docking and MD simulation are becoming a common protocol in computational medicinal plant research. After the virtual screening, docking will find the candidate compounds that can form favorable binding affinity, and the MD simulation will validate their existence and stability in time. This complementary approach minimizes false positive predictions and boosts the accuracy of lead prioritization. This has made molecular docking and MD simulations two invaluable tools in drug discovery from medicinal plants and as key tools in the development of novel phytopharmaceuticals (21–23).

3.4 QSAR and Pharmacophore Modeling

Among the various ligand-based computational techniques, quantitative structure–activity relationship (QSAR) and pharmacophore modeling are important ones that can be helpful in the drug discovery process from medicinal plants. The following approaches aim to draw correlations between the phytochemical structures and their biological activity, which allow

the prediction of the pharmacological activity in early stage. They decrease the amount of extensive experimental screening required, speed up the time to identify and optimize leads, and reduce research costs and time (24,25). QSAR modeling involves statistical and mathematical relationships between the molecular properties (hydrophobicity, electronic properties, molecular weight, hydrogen bonding capacity, topological indices, etc.) and the biological activity. Recent developments in machine learning have improved the accuracy of QSARs, facilities for analyzing complex phytochemical data. Currently, QSAR is extensively used in medicinal plant research to predict antioxidant, antimicrobial, anticancer, antiviral and anti-inflammatory activities, which facilitates the selection of compounds for further studies (24). Pharmacophore modeling is used in addition to QSAR to determine the structural features important for biological activity. These properties are: the presence of hydrogen bond donors and acceptors, the presence of hydrophobic groups, the presence of aromatic groups, and the presence of charged groups in specific spatial arrangements. Pharmacophore models can be used to screen databases of phytochemicals to find compounds that have similar functional features and thus may be able to inhibit enzymes, receptors, and signaling pathways, and this approach leads to the discovery of novel phytogenic inhibitors (24,25). The synergy of the QSAR and pharmacophore modeling and molecular docking with molecular dynamics simulation and artificial intelligence provides a comprehensive computational framework. The activity can be predicted by QSAR, the characteristic activity features are defined by pharmacophore modeling and docking validates activity features. These approaches can be combined to optimize lead identification and discovery of phytopharmaceutical drugs (24,25).

3.5 Network Pharmacology

Network pharmacology is a cutting-edge computational method overcoming the drawbacks of using the classic "one drug–one target" paradigm, which investigates intricate relationships between the phytochemicals, molecular targets, biological pathways, and diseases. In contrast to synthetic drugs, medicinal plants have several bioactive compounds, that can synergistically target different proteins and signaling pathways. This method gives a systemic picture of the more comprehensive therapeutic effects of herbal medicines and has turned into an important method in contemporary phytopharmaceutical investigations (26,27). The first step in the process of network pharmacology is to identify the bioactive phytochemicals from databases and literature mining. Predicted targets include the use of platforms like SwissTargetPrediction, STITCH, DrugBank and GeneCards. These targets are then linked in a database such as STRING to build a protein–protein interaction (PPI) network together with disease-related genes. The results of further analysis such as Kyoto Encyclopedia of Genes and Genomes (KEGG), Gene Ontology (GO) can help identify relevant biological processes and signaling pathways. This systematic workflow allows the discovery of the molecular mechanisms of the efficacy of medicinal plants (26–28). Network pharmacology has been extensively used to investigate the treatment of many diseases such as cancer, diabetes, cardiovascular diseases, inflammatory diseases, neurodegenerative diseases and viral diseases. It is integrated with molecular docking and molecular dynamics simulation, increasing prediction accuracy by validating phytochemical-target interactions. Moreover, with the development of AI and multi-omics technologies, this method has been reinforced to facilitate precision phytomedicine and personalized drug discovery (26-28).

4. PUBLIC DATABASES & DIGITAL RESOURCES

Publicly available chemical and biological databases have been growing rapidly and greatly improved medicinal plant research using computation tools that uses those databases, since they are the source of reliable repositories of phytochemicals, protein targets, pharmacological activities and pharmacokinetic properties. These resources are helpful for virtual screening, identification of targets, molecular docking, network pharmacology, and ADMET prediction, which helps to shorten the process of the discovery of therapeutic candidates from plants. The combination of these databases with AI and computer aided drug designing has created a powerful digital environment for effective phytopharmaceutical research (29,30). PubChem is one of the largest public repositories of chemical structures, bioassays, and molecular properties, and is a major source of information for identifying phytochemicals and virtual screening. ChEMBL is a curated database of bioactive molecules and their experimentally determined biological activities that can be used for drug–target interaction studies. Valuation for drug repurposing and target validation, DrugBank provides comprehensive drug, target and pharmacological information. There are several natural product specific databases such as NPASS, IMPPAT and TCMID that provide a large amount of information on phytochemicals, medicinal plants, traditional formulations, and related therapeutic activities that can be used for computational exploration of herbal medicine (29-31). The capabilities of computational drug discovery have been further enhanced by the use of specialized web servers. SwissADME is used to predict physicochemical parameters, pharmacokinetics,

drug-likeness and medicinal chemistry parameters, while SwissTargetPrediction is used to predict potential protein targets by the method of chemical similarity. The databases BindingDB and STRING can be used to gain information about protein–ligand interactions and protein–protein interaction networks, respectively, which can be used for systems-level analyses. Together, these digital resources facilitate easier access to information, increase computational accuracy, and facilitate reproducible research, and are essential in today's context of medicinal plant-based drug discovery (29–31).

Table 2. Major public databases and digital resources commonly used in computational medicinal plant research and natural product-based drug discovery.

Database	Primary Content	Major Application
PubChem	Chemical structures and bioassays	Compound identification and virtual screening
ChEMBL	Bioactive molecules and target information	Drug–target interaction studies
DrugBank	Drugs, targets, and pharmacological data	Drug repurposing and target validation
NPASS	Natural products and biological activities	Natural product screening
IMPPAT	Indian medicinal plants and phytochemicals	Phytochemical exploration
TCMID	Traditional Chinese medicine data	Herbal medicine research
SwissADME	Physicochemical and ADMET prediction	Drug-likeness and pharmacokinetic assessment
SwissTargetPrediction	Predicted protein targets	Target identification
BindingDB	Protein–ligand binding data	Molecular docking validation
STRING	Protein–protein interaction networks	Network pharmacology analysis

5. APPLICATIONS AND RECENT CASE STUDIES

The use of computational platforms has significantly broadened the opportunities for research on medicinal plants, allowing the identification of various bioactive compounds, therapeutic targets, and molecular mechanisms in a wide variety of diseases in an efficient manner. To enhance the efficiency and success rate of natural product-based drug discovery, complementary approaches such as artificial intelligence, molecular docking, network pharmacology and molecular dynamics simulations are increasingly used to prioritize phytochemicals before experimental testing (32, 33). In the field of oncology research, computational methods have helped in identifying plant constituents with high affinity to proteins that promote cell proliferation, apoptosis, angiogenesis, and metastasis. In order to predict the interactions of phytochemicals with the targets such as EGFR, PI3K/Akt, NF-κB, and VEGF signaling pathways, molecular docking and network pharmacology approach has been widely used to investigate the chemicals such as curcumin, quercetin, berberine, and withanolides. These studies have given mechanistic information that has helped to guide later in vitro and in vivo studies (32–34). Computational medicinal plant research has also been greatly involved in the identification of therapeutic candidates for metabolic and infectious diseases. Virtual screening and docking studies have revealed a plethora of phytochemicals that interact with α-glucosidase, dipeptidyl peptidase-4 (DPP-4), ACE2, viral proteases, and other clinically relevant targets connected to diabetes, hypertension and viral infections. As part of the COVID-19 pandemic, several natural compounds were quickly tested against SARS-CoV-2 proteins through the use of integrated computational workflows, highlighting the importance of in silico methods to speed up emergency

drug discovery (33-35). Artificial intelligence is being used in recent studies, alongside multi-step computational pipelines, such as virtual screening, molecular docking, molecular dynamics simulation, ADMET prediction, and network pharmacology. These integrated approaches are useful for better prioritization of leads, lowering false positive predictions and giving a holistic view of the drug potential of medicinal plants. In the future, further advances in the establishment of high-quality phytochemical databases and the development of predictive models for phytochemical characterization using artificial intelligence (AI) are likely to help link computational results to clinically relevant phytopharmaceuticals (34,35).

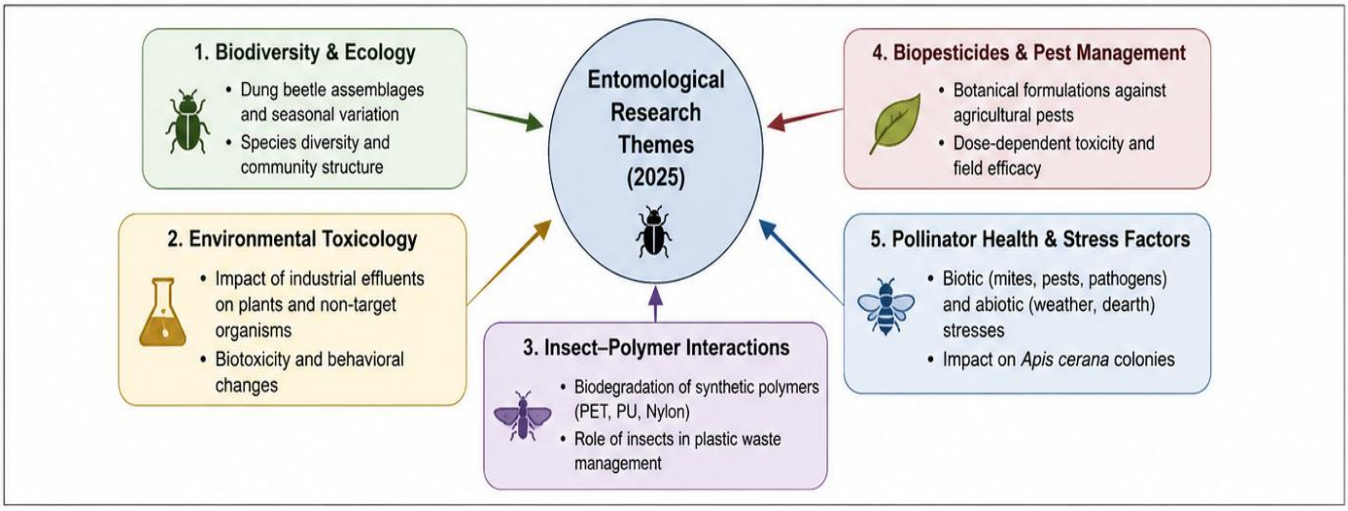

Figure 2. Integrated computational ecosystem for medicinal plant-based drug discovery

6. CHALLENGES AND FUTURE PERSPECTIVES

Although there has been significant progress in computational technologies to date, some challenges remain to be addressed to make these technologies broadly applicable in the study of medicinal plants. The lack of complete and standardized, experimentally verified phytochemical data is one of the largest challenges. A large number of medicinal plants are still not chemically studied and databases are often not complete, with names that are not consistent or with insufficient pharmacological data. These constraints limit the predictive power and applicability of artificial intelligence (AI) and machine learning (ML) models and highlight the need for high-quality and curated datasets that capture the chemical diversity of medicinal plants (36,37). An additional challenge is the trustworthiness and understanding of computational predictions. Using suitable validation strategies, molecular docking, QSAR, and machine learning models can yield a false-positive prediction. In addition, a number of deep learning algorithms are "black box" systems where it is hard to interpret why a system makes a prediction. Enhanced transparency, reproducibility, and trust in computational drug discovery will therefore depend on development of explainable artificial intelligence (XAI), standardized computational workflows, and rigorous benchmarking protocols (36–38). While computational methods can definitely save a lot of time and money during the initial stages of drug discovery, experimental validation is a must. Before clinical use, the predicted phytochemicals should be thoroughly investigated via in vitro, in vivo, pharmacokinetic and toxicological studies. Incorporating computational scientists, pharmacologists, medicinal chemists, and clinicians into one team will help translate computational discoveries into safe and effective plant-derived therapeutics (37,39). For the future, research is likely to focus on the intersection of AI, multi-omics technologies, high-performance computing, cloud-based solutions, and digital health systems. New technologies like generative AI, graph neural networks, AlphaFold protein structure prediction, digital twins, and federated learning will also enhance the identification of targets, lead optimization, and personalized phytomedicine. Furthermore, broadening the availability of publicly accessible phytochemical databases and encouraging open data initiatives will increase the ability to facilitate collaborative research and improve the repetition of computational research. Together, these innovations can help to make medicinal plant research more predictive, data-driven, and precision-oriented, consequently leading to the development of novel phytopharmaceuticals for the prevention and treatment of complex human diseases (38–40).

7. CONCLUSION

The emergence of new computational platforms has revolutionized the study of medicinal plants, allowing for more rapid, accurate and cost-effective identification of compounds with medicinal properties from these plants. The use of artificial intelligence, machine learning, computer-aided drug design, molecular docking, molecular dynamics simulation, QSAR, network pharmacology and digital databases have greatly facilitated the identification, characterization and optimization of bioactive phytochemicals. These computational methods can be used alongside traditional pharmacognostic and experimental techniques; they enable virtual screening of complex libraries, prediction of targets, exploration of mechanisms and testing of the pharmacokinetic and toxicological properties of compounds early in the drug discovery process, which means that they can save time and resources. Despite these advances, issues of data quality, model interpretability, database standardization and experimental validation remain, limiting the broader clinical utility of computational predictions. The solution of these problems will involve the collaboration of computational scientists, medicinal chemists, pharmacologists, and the bioinformaticians and clinicians. Moreover, the rapid advancement of explainable artificial intelligence, the integration of multi-omics, high-performance computing, and open-access phytochemical databases will further ensure the reliability and applicability of computational medicinal plant studies. To sum up, the era of computational platforms in the field of natural product-based drug discovery is reshaping the way the field is approached, fusing centuries-old medicinal wisdom with contemporary digital solutions. They will further help to create safer, more efficient and scientifically proven phytopharmaceuticals and they will help in precision medicine and sustainable drug discovery. Medicinal plants are likely to remain a valuable resource for discovering new medications to combat future and present global health problems as computational and experimental approaches become more intertwined.

DECLARATIONS

Funding: The authors received no specific financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Author Contributions: All authors contributed substantially to the conception, literature review, manuscript preparation, critical revision, and approval of the final version of the manuscript.

Ethical Approval: Ethical approval was not required because this study is a review article based exclusively on published literature.

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