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Structure-Based Computational Design of Plant-Derived Therapeutic Agents

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ABSTRACT: Although the new target molecules have been identified from H. sapiens, the bioactive molecules obtained from plants are still the precious source for discovery of new therapeutic agents because of their structural diversity and vast pharmacological activities. In recent years, the study of natural products has been revolutionized by the possibility of using molecular docking, molecular dynamics simulations, pharmacophore modeling, virtual screening, quantitative structure–activity relationship (QSAR) analysis, binding free-energy calculations, and artificial intelligence (AI) approaches to advance the process of drug discovery. These computational methodologies have been useful in the development of efficient drug discovery tools for identification of drug targets, lead optimization, prediction of ADMET properties and rational design of drug therapeutics based on phytochemicals and reducing the cost and time of experimental drug discovery. Furthermore, AI, machine learning and multi-omics integration has enhanced the predictive capabilities and has enabled precision medicine applications in cancer, neurodegenerative diseases, cardiovascular, metabolic, infectious, and inflammatory diseases. While there are hurdles to address, such as the need for higher-quality structural data, a better understanding of protein flexibility, and the ability to validate experimental results, the potential for personalized phytopharmaceutical development continues to grow thanks to ongoing developments in the fields of computational biology and explainable AI. The principles, methodologies, applications, challenges and future

prospects of structure-based computational approaches to discovery and optimization of plant-based therapeutic agents are highlighted in this chapter.

1. INTRODUCTION

The use of therapeutic agents from plants, which provide structurally different bioactive compounds with high pharmacological significance in the prevention, diagnosis and treatment of many human diseases, has had a decisive influence on the discovery and development of the modern drugs. Natural products such as alkaloids, flavonoids, terpenoids, polyphenols, glycosides, and phenolic acids show noteworthy biological specificity and chemical diversity that has afforded a rich source of useful lead compounds for a range of drugs including those for anti-cancer, antimicrobial, antiviral, anti-inflammatory, cardioprotective, and neuroprotective applications (1). Traditional natural product-based drug discovery, however, suffers from various drawbacks such as time-consuming and cost intensive experiments, low success rate and challenges in identifying the molecular target and improving on the lead compound. Recent advances in computational drug discovery have revolutionized the process by integrating bioinformatics, structural biology, cheminformatics, molecular modeling, and artificial intelligence to quickly discover new compounds that have potential therapeutic applications and to optimize compounds derived from plants to maximize therapeutic benefits (2). One of these methods has proven to be one of the most powerful computational strategies, Structure-Based Drug Design (SBDD), which studies the interaction between a protein and a ligand at the atomic level, with the help of the 3D structure of the biological target. In the drug development area, SBDD enables scientists to predict the binding affinity, binding mode, molecular stability, structure-activity relationship (SAR), and calculate binding free energy with methods including molecular docking, molecular dynamics simulation, pharmacophore modeling, virtual screening, binding free energy calculation, and structure-guided lead optimization, which help lower the time, cost, and resources required before experimental validation. (3)The integration of high-resolution protein structural data, extensive phytochemical databases, and advanced computational algorithms has further improved the precision of identifying promising phytochemicals with enhanced selectivity, reduced toxicity, and favorable pharmacokinetic properties. Consequently, computational structure-based approaches have become indispensable tools for translating traditional medicinal knowledge into scientifically validated therapeutic candidates. This chapter aims to provide a comprehensive overview of the principles, methodologies, applications, advantages, and recent advances in structure-based computational design of plant-derived therapeutic agents while highlighting emerging technologies, current challenges, and future opportunities for precision natural product drug discovery and rational phytopharmaceutical development (4).

2. PLANT-DERIVED BIOACTIVE COMPOUNDS IN DRUG DISCOVERY

The bioactive compounds found in plants are one of the best sources of structurally diverse compounds with several biological activities, which are challenging to synthesize and are not found in any other source. Phytochemicals like alkaloids, flavonoids, terpenoids, phenolic acids, lignans, coumarins, saponins, tannins, glycosides and essential oils have been shown to have remarkable therapeutic potential against a wide range of diseases, including cancer, cardiovascular disorders, diabetes, neurodegenerative diseases, infectious diseases, and chronic inflammatory diseases. The secondary metabolites of these naturally occurring plants have antioxidant, antimicrobial, antiviral, anticancer, anti-inflammatory, immunomodulatory and cardioprotective properties, which makes them good lead compounds to develop new pharmaceuticals (4). Plant secondary metabolites are usually divided into three major groups on the basis of their biosynthetic origin and chemical structure: terpenoids, phenolic compounds and nitrogen-containing compounds (alkaloids). The molecular properties and mechanism of action of each class are quite different, allowing for selective modulation of enzymes, receptors, ion channels and signaling pathways/sign transduction, as well as transcription factors that drive disease progression (5). Plant-derived bioactive compounds have been translated to highly effective therapeutic agents with large number of clinically used drugs like paclitaxel, vincristine, vinblastine, artemisinin, camptothecin derivatives and morphine (6). The structural complexity of phytochemicals, experimental screening and target validation (which is time consuming), isolation and purification difficulties, low aqueous solubility, and low bioavailability are still problematic in natural product-based drug discovery. Natural product composition variations based on environment and geographical location continue to pose challenges. The limited supply of bioactive constituents is still a challenge. Furthermore, the mode of action of potentially interesting phytochemicals is still being

investigated, and the production in larger scale in the current production techniques has challenges with rapid clinical translation. But, in the age of computational approaches, high-throughput screening technologies, metabolomics and AI, the identification, characterization and optimization of plantderived lead compounds are now becoming more efficient, and can help to identify safe and effective, clinically relevant therapeutics from natural sources, which would overcome these limitations (7).

3. PRINCIPLES OF STRUCTURE-BASED DRUG DESIGN

Structure Based Drug Design (SBDD) is a rational computational approach that takes advantage of the 3-D structure of biological macromolecules to design and optimize therapeutic compounds of high specificity and affinity. Understanding the structural architecture of target protein(s) and the small molecule interactions at the atomic level are central to SBDD. High resolution protein structures obtained from X-ray crystallography, nuclear magnetic resonance (NMR) and cryo-electron microscopy (cryo-EM) or accurately predicted by the use of tools developed based on AI allow detailed characterization of molecular recognition mechanisms and active sites. The key properties for selective protein–ligand recognition and biological activity, such as complementary structural, electrostatic and physicochemical properties are essential for identification of plant derived bioactive compounds as therapeutic agents (7). Identification and validation of suitable drugs targets is a critical part of the SBDD, in which proteins that are involved in the initiation or progression of disease, while being therapeutically relevant, structurally accessible and have minimal off-target effects, are selected. Incorporation of functional genomics, proteomics, systems biology, and pathway analysis with structural biology are increasingly being combined to prioritize disease-associated targets that are appropriate for computational investigation (8). After target selection, binding pocket analysis is carried out to find out all the ligand accessible cavities, catalytic residues, allosteric sites and physicochemical properties which affect the binding of the ligands. The computational algorithms are sophisticated, and they will consider the size, shape, hydrophobicity, flexibility and composition of the residue in the pocket, useful for virtual screening and for lead optimization. A precise characterization of the binding pockets can greatly help identify phytochemicals possessing the desired binding properties and selectivity (9). The binding affinity and therapeutic activity of any ligand to its target protein are at the end determined by molecular interactions. Examples of these include hydrogen bonding, hydrophobic contacts, electrostatic attraction, van der Waals attraction, π–π stacking, salt bridges, and water-mediated interactions, which all contribute to the formation of protein–ligand complexes and are important for protein function. Rational lead optimization and lower experimental costs can be achieved through computational approaches like molecular docking, molecular dynamics simulations, and calculation of binding free energy to quantitatively evaluate these interactions. Finally, the workflow of these inter-connected computational processes involved in identification, evaluation and optimization of plant derived therapeutic candidates was presented in Figure 1 that depicts the general structure of the comprehensive target selection to lead optimization to experimental validation (10) based on a computational drug discovery pipeline.

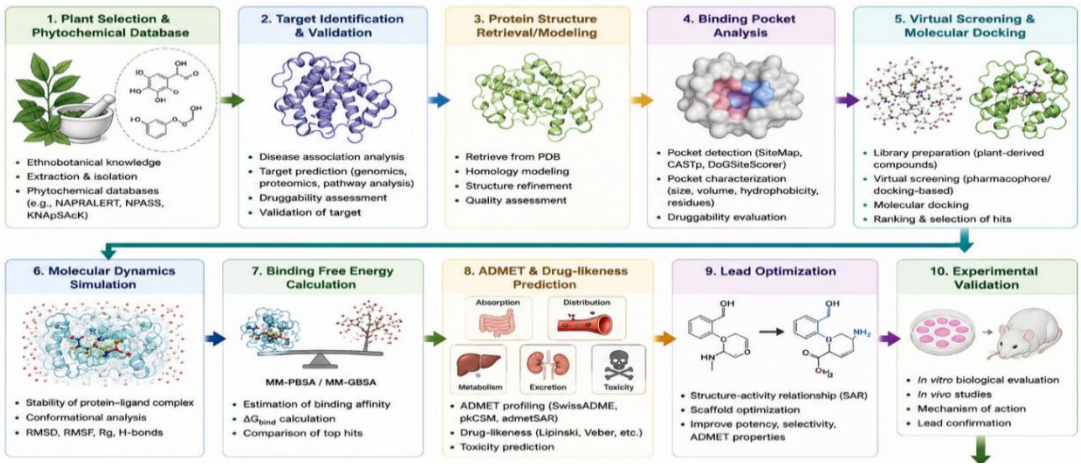

Figure 2. Workflow of Structure-Based Drug Discovery Using Molecular Docking, Molecular Dynamics, and ADMET Prediction.

4. COMPUTATIONAL TECHNIQUES IN STRUCTURE-BASED DESIGN

Structure based drug design (SBDD) is a combination of several computational methods that helps to speed up the identification, assessment and optimization of plant derived bioactive molecules for therapeutic use. One of the most common techniques employed in the prediction of most suitable orientation and binding strength of phytochemical in target proteins' active site is molecular docking. The interactions which a protein makes with a ligand can involve hydrogen bonds, hydrophobic interactions, electrostatic forces, π–π stacking and van der Waals interactions, and can be easily calculated by docking algorithms, which allow compounds with a high binding potential to be quickly prioritized for experimental testing before testing more compounds (11).Molecular docking can provide a snapshot view of the ligand binding while molecular dynamics (MD) simulation can provide a dynamic view by examining the stability, flexibility and conformational changes of protein–ligand complexes over the course of time under physiological conditions. MD simulations can give detailed information on the changes in structure, the persistence of hydrogen bonds, solvent interaction, root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg) and conformational stability, which helps to strengthen the level of confidence in a docking prediction and facilitates the identification of stable therapeutic candidates (12). The benefits of pharmacophore modeling for lead discovery are further increased by providing information about the necessary steric and electronic properties for biological activity, such as hydrogen bond donors and acceptors, aromatic rings, hydrophobic regions and charged functional groups. Pharmacophore-based virtual screening can help to build a large library of phytochemical compounds having the desired molecular properties and deliver structurally diverse compounds. To this end, the Quantitative Structure–Activity Relationship (QSAR) modelling has been developed, which correlates the biological activity of molecules with their basic chemical structure in order to predict the potency, toxicity and physicochemical properties of new phytochemicals without extensive laboratory testing. QSAR is an important tool for rational optimization of leads which minimizes the number of costly experimental screening required (13). Virtual screening combines docking, pharmacophore modeling and machine learning algorithms to screen thousands of natural products against a desired therapeutic target in a short time, which saves time and resources during the lead identification process. Finally, free energy of binding for ligands calculated using Molecular Mechanics/Poisson–Boltzmann Surface Area (MM-PBSA) and Molecular Mechanics/Generalized Born Surface Area (MM-GBSA) to derive quantitative estimates of affinity of the ligand for the receptor. These calculations can be used to improve hit prioritization and help with optimal lead optimization before experimental studies. All of these complementary computational methods as a whole form the backbone of the modern computational drug discovery and are relatively efficient in the development of safe, potent and selective plant-based therapeutic agents in different human diseases (14).

5. ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN STRUCTURE-BASED DRUG DESIGN

Artificial intelligence (AI) and machine learning (ML) have transformed structure-based drug design by enabling rapid analysis of complex biological data, improving predictive accuracy, and accelerating the discovery of plant-derived therapeutic agents. AI-assisted computational platforms integrate structural biology, cheminformatics, genomics, and pharmacological data to identify disease-associated drug targets with greater speed and precision than conventional experimental approaches. Machine learning algorithms analyze protein sequences, structural features, gene expression profiles, protein–protein interaction networks, and biological pathways to predict novel therapeutic targets and prioritize proteins with high druggability, thereby significantly reducing the time required for target identification and validation (14). Deep learning has further expanded the capabilities of molecular design by employing advanced neural network architectures, including graph neural networks (GNNs), convolutional neural networks (CNNs), recurrent neural networks (RNNs), and transformer-based models, to predict molecular properties, protein–ligand interactions, binding affinities, toxicity profiles, and pharmacokinetic characteristics. These models learn complex structural patterns from extensive chemical and biological datasets, enabling accurate prediction of bioactive phytochemicals and facilitating rational molecular optimization (15). Recent advances in **generative artificial intelligence** have introduced powerful frameworks such as variational autoencoders (VAEs), generative adversarial networks (GANs), diffusion models, and large language models capable of designing novel molecules with predefined physicochemical, pharmacological, and ADMET properties. These generative models optimize lead compounds by modifying molecular scaffolds, improving target selectivity, enhancing binding affinity, and minimizing toxicity while maintaining structural diversity, thereby accelerating lead optimization and reducing costly iterative synthesis (16). Furthermore, the integration of **multi-omics data**, including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiomics, has enabled a systems-level understanding of disease mechanisms and therapeutic responses. AI algorithms efficiently integrate these heterogeneous datasets to identify disease biomarkers, uncover molecular pathways, predict therapeutic targets, and support precision medicine

strategies tailored to individual patients (17). Coupled with high-performance computing, cloud-based platforms, and explainable AI methodologies, these technologies improve model transparency, reproducibility, and clinical applicability while enhancing confidence in computational predictions (18). Consequently, AI-driven structure-based drug design has become a cornerstone of modern computational phytopharmaceutical research, enabling efficient discovery, optimization, and personalized development of plant-derived therapeutic agents with improved efficacy, safety, and translational potential, thereby reshaping the future of precision drug discovery and natural product-based therapeutics (19).

6. ADMET AND DRUG-LIKENESS PREDICTION

Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties are critical in structure-based drug design as many promising lead compounds are not developed to market because of poor pharmacokinetic properties or unacceptable toxicity. Computational ADMET will help to identify compounds with favorable drug-like properties early in the development process and reduce the cost of development and prevent compounds from failing while in late development. Intestinal absorption and membrane permeability, volume of distribution, plasma protein binding, metabolic stability, cytochrome P450 interactions, renal clearance and elimination profiles are predicted using advanced in silico tools for pharmacokinetic evaluation. These forecasts help researchers to choose plant-based bioactive molecules that are more likely to have desirable pharmacokinetic properties prior to experimental evaluation and help to enhance the efficiency of lead optimization (19). Machine learning and quantitative structure–activity relationship (QSAR) models are essential tools for the prediction of toxicity in computational drug discovery, enabling the rapid assessment of important toxicity endpoints such as hepatotoxicity, cardiotoxicity, nephrotoxicity, mutagenicity, carcinogenicity, reproductive toxicity, skin sensitization, and acute oral toxicity. Structural changes to improve the safety of the compound while maintaining its biological activity can occur with the discovery of toxic liabilities, as described above (20).Generally, the drug-likeness assessment is done by Lipinski's Rule of Five which relies on molecular weight, lipophilicity (LogP), hydrogen bond donors, hydrogen bond acceptors, and molecular flexibility. Various other molecular parameters including Veber's, Ghose's, Egan's, Muegge's are also employed to assess molecular properties that would be desirable for good absorption and pharmacokinetic properties. These computational filters are especially useful for prioritising phytochemicals with suitable physicochemical characteristics for pharmaceutical development (21). Bioavailability and overall safety assessment is a combination of several computer models which estimate gastrointestinal absorption, blood–brain barrier permeability, P-glycoprotein interactions, oral bioavailability, bioavailability scores, metabolic liability, and adverse drug reaction. A number of computational platforms, such as SwissADME, pkCSM, admetSAR or ProTox-II, provides all of the information necessary for rational lead selection and lead optimization, reducing the need for large animal experiments (22). The recent advancements in AI, deep learning, and large pharmacological databases have further bolstered the precision and reliability of ADMET prediction by capturing intricate connections between molecular architecture and biological responses, aiding decision-making across the entire drug discovery process (23). The main computational tools employed in structure-based design, the main use of said tools, the most popular software tools and the results they can yield, are summarized in Table 1 in the context of computational phytopharmaceutical research (24).

Table 1. Major Computational Tools Used in Structure-Based Design of Plant-Derived Therapeutic Agents

Computational Method	Primary Purpose	Common Software	Output
Molecular Docking	Predict ligand binding	AutoDock, AutoDock Vina, Glide	Binding affinity and binding pose
Molecular Dynamics	Analyze complex stability	GROMACS, AMBER, NAMD	Structural stability and conformational dynamics
Virtual Screening	Screen large compound libraries	PyRx, Schrödinger Suite	Identification of lead compounds
Pharmacophore Modeling	Identify essential molecular features	LigandScout, Discovery Studio	Pharmacophore model

QSAR Analysis	Predict biological activity	OECD QSAR Toolbox, MOE	Activity and toxicity prediction
ADMET Prediction	Evaluate pharmacokinetics and toxicity	SwissADME, pkCSM, admetSAR, ProTox-II	Drug-likeness and ADMET profile
Binding Free Energy	Estimate binding strength	MM-PBSA, MM-GBSA	Binding free energy values
AI-Based Drug Design	Lead optimization and molecular generation	DeepChem, AlphaFold, ChemBERTa	Optimized therapeutic candidates

7. APPLICATIONS IN DISEASE-SPECIFIC DRUG DISCOVERY

Now, with the help of artificial intelligence, structure-based computational drug design has expanded the use of bioactive compounds from plants to the therapeutic discovery of new drugs for diseases, and enables rapid identification of molecular targets, optimization of lead compounds, and prediction of pharmacological efficacy. In the cancer therapeutics area, computer-based models have identified phytochemicals which can bind to oncogenic proteins like the epidermal growth factor receptor (EGFR), phosphatidylinositol-3-kinase/activated T-cell (PI3K/Akt/mTOR), Bcl-2, vascular endothelial growth factor receptor (VEGFR), and p53 signaling pathways. The molecular docking, molecular dynamics simulation and AI virtual screening assists in identifying powerful anticancer agents that are more selective and have less toxicity (24). Neurodegenerative diseases: Plant chemical constituents are virtually screened against target molecules in Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. AI models have been successful in predicting the blood–brain barrier penetration and possible neuroprotective properties of phytochemicals (25) and structure-based studies have identified numerous inhibitors of acetylcholinesterase (AChE), beta-secretase (BACE1), monoamine oxidase, aggregation of α-synuclein, and phosphorylation of tau proteins (24). There have also been advances in computational approaches that have aided in the identification of plant-based drugs for cardiovascular conditions, such as flavonoids, phenols and terpenoids that are studied for their potential to control the activity of angiotensin-converting enzyme (ACE), HMG-CoA reductase, cyclooxygenase (COX), endothelial nitric oxide synthase (eNOS), and inflammatory markers associated with hypertension, atherosclerosis and myocardial damage (26). Similarly, the natural compounds with anti-α-glucosidase, anti-α-amylase, anti-DPP-4, anti-PPAR-γ, anti-glucokinase and anti-insulin signaling activities to modulate glucose, insulin sensitivity and lipid metabolism would be beneficial for the treatment of diabetes and metabolic disorders and could be screened by AI. The following computation methods are useful in the search for multi-target phytochemicals that are able to inhibit a complex metabolic disease (27). Furthermore, plant-derived bioactive molecules have been found to possess therapeutic potential against infectious diseases, including bacterial, viral, fungal, and parasitic infections, such as SARS-CoV-2 main protease, HIV protease, influenza neuraminidase, and bacterial DNA gyrase, by a computational approach. Phytochemicals for inflammatory & immune-mediated disorders are designed to inhibit NF-κB, COX-2, TNF-α, IL-6, JAK/STAT and MAPK signaling pathways to help manage chronic inflammation and immune dysfunction. The novel application of AI, multi-omics analysis, molecular docking, molecular dynamics simulations, and predictive pharmacology in the development of novel plant-derived therapeutic agents for precision medicine application targeting multiple disease conditions is shown in Figure 2 (28).

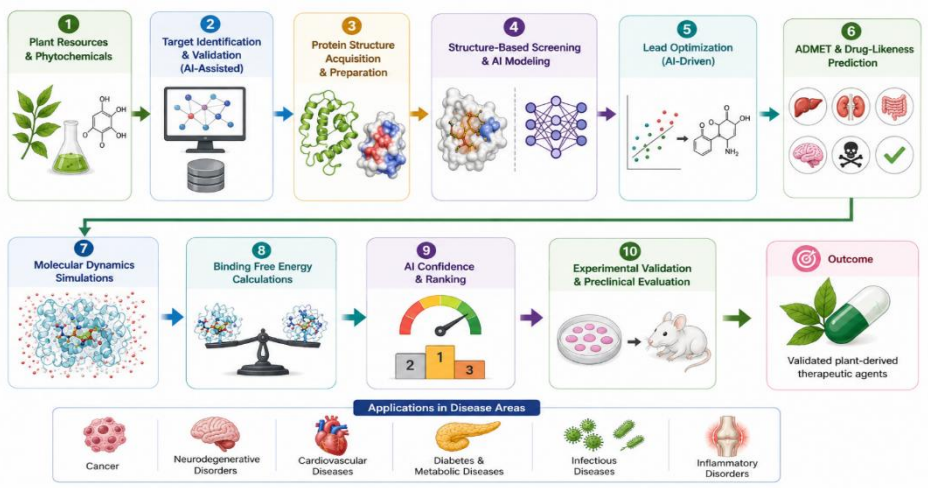

Figure 3. Integrated AI-Assisted Pipeline for Phytochemical Screening, Molecular Modeling, and Drug Development.

8. CHALLENGES, LIMITATIONS, AND FUTURE PERSPECTIVES

Although it has made tremendous progress in structure-based computational drug design, there are still some issues in the field of phytopharmaceutical research that hinder the broad use of this method. The prediction accuracy is sometimes limited by low number of good quality experimental protein structures and the lack of characterisation of plant phytochemicals, as well as the flexibility of the protein. Computational models must be well validated in an experimental manner prior to clinical translation. Furthermore, many AI algorithms are deemed as "black-boxes" and there is a need for Explainable AI (XAI) to boost transparency, reproducibility and regulatory acceptance. Future research may integrate this combination of advanced molecular simulations, multi-omics data, generative AI and precision medicine strategies to aid in the discovery of more relevant, efficient and personalized plant-derived therapeutics.

9. CONCLUSION

Structure-based computational design has revolutionized the process of discovering plant-derived therapeutic agents by integrating molecular modeling, AI and bioinformatics into a rational drug development process. The computational methods such as molecular docking, molecular dynamics, virtual screening, QSAR, ADMET prediction, and AI-driven lead optimization shorten the development timeline and lower costs and facilitate the identification of safe and effective phytochemicals. These strategies have proven effective to date in cancer, neurodegenerative, cardiovascular, metabolic, infectious and inflammatory diseases and hold great promise. Advances in explainable AI, structural biology, and precision medicine will continue to provide support to computational phytopharmaceutical research and will help develop a personalized, evidence-based natural product therapeutics.

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Ethical Approval: Not applicable, as this study is based solely on published literature.

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