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COMPUTER-AIDED NATURAL PRODUCT DRUG DISCOVERY: FROM VIRTUAL SCREENING TO LEAD OPTIMIZATION

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ABSTRACT

Computer-aided drug discovery (CADD) has emerged as an indispensable tool in natural product research, dramatically accelerating the identification and optimization of bioactive compounds from complex natural sources. The integration of computational approaches with experimental natural product chemistry has transformed traditional discovery paradigms, enabling the rapid exploration of vast chemical space and the prioritization of promising candidates for experimental validation. This review comprehensively examines the application of CADD methodologies in natural product drug discovery, focusing on structure-based approaches (molecular docking and molecular dynamics) and ligand-based approaches (pharmacophore modeling and quantitative structure-activity relationship analysis). We critically evaluate the strengths and limitations of these computational tools in the context of natural product libraries, addressing challenges including conformational flexibility, stereochemical complexity, and the unique physicochemical properties of natural products. Furthermore, we assess the integration of early-stage ADMET prediction and the corroborative in-silico and experimental approaches that validate computational predictions. Despite significant advances, challenges including the accuracy of scoring functions, representation of natural product chemical space, and experimental validation requirements persist. This review identifies emerging trends and discusses strategies for optimizing CADD applications in natural product drug discovery.

Keywords: Computer-Aided Drug Discovery; Virtual Screening; Molecular Docking; Pharmacophore Modeling; QSAR; Natural Products

1 INTRODUCTION

Natural products have historically been the most productive source of drug leads, contributing to approximately 60% of approved small-molecule drugs (Newman and Cragg, 2020). The structural complexity and diversity of natural products, characterized by unique scaffolds and stereochemical configurations, offer unparalleled opportunities for targeting challenging biological targets (Atanasov et al., 2021). However, traditional natural product discovery approaches—involving extraction, bioactivity-guided fractionation, and structure elucidation—are time-consuming, resource-intensive, and limited by the vast chemical complexity of natural sources (Harvey et al., 2015).

The conventional drug development pathway has several limitations, including high cost and time required to validate a drug through clinical trial phases. The average funding needed to develop a drug ranges from $897 million to $1.9

billion, with the process taking between 10 to 15 years (Computational Pharmacology and In Silico Clinical Trials, 2023). Despite the substantial amount of time and investment made from drug discovery to market, the success rate remains low, noted as <10% (Computational Pharmacology and In Silico Clinical Trials, 2023). Natural products are further limited by the difficulty in isolating and identifying active molecules, necessitating the application of computational approaches to streamline the discovery process (Computational Pharmacology and In Silico Clinical Trials, 2023).

Computer-aided drug discovery has emerged as a transformative approach in natural product research, enabling the efficient exploration of chemical space and the prioritization of compounds for experimental investigation (Simoben et al., 2023). In silico-based methods have been shown to play a pivotal role in modern pharmaceutical drug discovery processes. The application of these methods in identifying natural product-based hits has been successful, particularly in research setups that use rationally in silico-based methods in combination with experimental validation techniques (Simoben et al., 2023). Computational approaches such as molecular docking, pharmacophore modeling, quantitative structure-activity relationship analysis, absorption-distribution-metabolism-excretion-toxicity prediction, and molecular dynamics simulations have been applied in natural products-based drug discovery (Computational Pharmacology and In Silico Clinical Trials, 2023).

In recent years, the growth of computational approaches like virtual screening, molecular dynamics, pharmacophore modelling, Quantitative structure–activity relationship, ADMET, network biology, and machine learning has gained importance due to their efficiency, reduced time-consuming nature, and cost-effectiveness (Recent advances in plant-based anti-cancer drug discovery, 2023). The combination of in silico and in vitro approaches has rendered the use of in silico-based approaches even more popular and successful in the investigation of natural products (Simoben et al., 2023).

This review provides a comprehensive examination of CADD methodologies in natural product drug discovery, evaluating their applications, strengths, and limitations. We discuss the technicalities, limitations, and successful applications of key components of structure-based (molecular docking and molecular dynamics) and ligand-based (quantitative structure–activity relationship and pharmacophore modeling) approaches in medicinal plant-derived drug discovery (From roots to codes, 2023).

2 STRUCTURE-BASED VIRTUAL SCREENING AND MOLECULAR DOCKING

2.1 Principles of Structure-Based Drug Design

Structure-based virtual screening (SBVS) is primarily conducted using molecular docking, which enhances high-throughput virtual screening procedures (Integrative strategies in herbal product-based drug discovery, 2023). Structure- and ligand-based modeling are vital pillars of in-silico drug discovery (From roots to codes, 2023). Structure-based approaches rely on the three-dimensional structures of target proteins, obtained through X-ray crystallography, NMR spectroscopy, or homology modeling, to predict the binding modes and affinities of small molecules.

The fundamental principle of molecular docking is to predict the preferred orientation of a ligand when bound to a protein target, thereby estimating the binding affinity and identifying the most favorable binding conformations (Simoben et al., 2023). This approach enables the virtual screening of large compound libraries, prioritizing candidates with the highest predicted binding affinity for experimental validation.

Molecular docking and virtual screening are computational techniques that have proven invaluable in the identification of potential lead compounds in drug discovery (Computational Pharmacology and In Silico Clinical Trials, 2023). The application of these methods to natural product libraries has enabled the rapid identification of bioactive compounds from vast chemical spaces that would be impractical to screen experimentally.

2.2 Docking Algorithms and Scoring Functions

Molecular docking algorithms are broadly classified into two categories: incremental construction algorithms and metaheuristics-based algorithms. Incremental construction algorithms build ligand conformations incrementally within the binding site, while metaheuristics-based algorithms employ genetic algorithms or simulated annealing for conformational search. The selection of appropriate docking algorithms depends on the specific application and target.

Scoring functions evaluate the binding affinity of docked poses and are critical for compound ranking. These functions can be categorized as force field-based, empirical, or knowledge-based, each with distinct advantages and limitations. Force field-based scoring functions, including MM-GBSA and MM-PBSA, provide accurate energetic evaluations but are computationally intensive. Empirical scoring functions, including ChemScore and GlideScore, utilize experimentally derived parameters for rapid evaluation. Knowledge-based scoring functions utilize statistical potentials derived from protein-ligand complex structures.

Consensus scoring, combining multiple scoring functions, improves prediction reliability by leveraging the strengths of different approaches. This strategy has been particularly valuable in natural product docking, where the unique physicochemical properties of natural products may not be optimally represented by any single scoring function.

2.3 Challenges in Natural Product Docking

Natural products present unique challenges for molecular docking (Simoben et al., 2023). The conformational flexibility of natural products, with multiple rotatable bonds and stereocenters, increases computational complexity. The unique physicochemical properties of natural products, including high molecular weight and hydrogen bond donor/acceptor counts, may not be well represented by scoring functions trained on synthetic compounds.

Identifying and proposing novel natural product-based hits for experimental validation comes with several challenges such as the availability of compounds by suppliers, the huge task of separating pure compounds from complex mixtures, the quantity of samples available from the natural source to be tested, not to mention the potential ecological impact if the natural source is exhausted (Simoben et al., 2023). Because most peer-reviewed publications are biased towards "positive results", these challenges are generally not discussed in publications (Simoben et al., 2023).

The presence of multiple stereocenters requires the consideration of stereoisomers, significantly increasing the computational burden. Furthermore, the representation of natural product chemical space in docking libraries remains incomplete, with many databases lacking comprehensive coverage of the structural diversity found in nature.

2.4 Integration with Experimental Approaches

The integration of molecular docking with experimental approaches enhances discovery efficiency. Docking results guide bioactivity screening, reducing the number of compounds requiring experimental testing. Experimental validation of docking predictions provides feedback for refining computational models. The development of integrated workflows combining computational and experimental approaches is increasingly common.

The combination of in silico-based approaches with experimental validation techniques has rendered the use of in silico-based approaches even more popular and successful in the investigation of natural products (Simoben et al., 2023). This integrated approach allows researchers to leverage the efficiency of computational screening while confirming predictions through rigorous experimental testing.

Table 1: Comparison of Structure-Based Virtual Screening Approaches for Natural Products

Approach	Principle	Strengths	Limitations	Suitability
Molecular Docking	Binding pose and affinity prediction	Mechanistic basis, target structure utilization	Scoring function accuracy, conformational sampling	Target structure known
Molecular Dynamics	Protein-ligand complex simulation	Dynamic behavior, conformational changes	Computationally intensive	Refinement of docking poses
MM-GBSA/PBSA	Free energy calculation	Accurate binding energy estimation	Computationally expensive	Lead optimization
Consensus Scoring	Multiple scoring functions	Improved prediction reliability	Requires multiple tools	Hit prioritization

3 LIGAND-BASED VIRTUAL SCREENING APPROACHES

3.1 Pharmacophore Modeling

Pharmacophore modeling identifies the three-dimensional arrangement of chemical features essential for biological activity. When a ligand-based virtual screening approach is required, options include pharmacophore modelling, quantitative structure–activity relationship (QSAR), and structural similarity searching models (Integrative strategies in herbal product-based drug discovery, 2023). Pharmacophore models can be generated from either the target binding site structure (structure-based) or from a set of known active compounds (ligand-based).

Structure-based pharmacophore generation utilizes the binding site structure to identify critical interactions between the target and potential ligands. Ligand-based pharmacophore generation employs a set of known active compounds to

identify common features essential for activity. Machine learning approaches have been applied to pharmacophore generation, improving predictive accuracy.

Focusing on 3D pharmacophore modeling techniques, virtual screening filtering experiments using pharmacophore models, docking studies, and neural networks help to establish a relationship between chemical structure and biological activity (Strategies for Efficient Lead Structure Discovery, 2022). These approaches have been successfully applied to the discovery of bioactive natural products, including inhibitors of cyclooxygenase and lipoxygenase (Strategies for Efficient Lead Structure Discovery, 2022).

Pharmacophore-based virtual screening has been employed to identify bioactive natural products through the application of modern in-silico molecular modeling techniques (Identification of Bioactive Natural Products by Pharmacophore-Based Virtual Screening, 2022). These strategies discuss how to discover and optimize drug candidates inspired by nature, leveraging the power of 3D pharmacophore modeling to navigate natural product chemical space efficiently.

3.2 Quantitative Structure-Activity Relationship (QSAR)

Quantitative structure-activity relationship (QSAR) approaches correlate chemical structure with biological activity, enabling the prediction of activity for untested compounds. Classical QSAR employs physicochemical descriptors and regression models, while 3D-QSAR methods, including CoMFA and CoMSIA, incorporate three-dimensional structural information.

The application of molecular docking, QSAR modeling, and molecular dynamics simulations supports the evaluation and optimization of phytochemicals as potential drug candidates (Integrating phytochemicals and in silico methods, 2023). QSAR models enable the prediction of biological activity based on chemical structure, facilitating the prioritization of compounds for experimental testing and guiding lead optimization efforts.

SAR and QSAR studies on various compound classes have provided valuable insights into the relationship between anticancer activity and molecular structure, enabling the rational design of more potent derivatives (SAR and QSAR studies on pentacyclic triterpenes, 2023). The integration of QSAR with other computational approaches enhances the efficiency of natural product drug discovery.

3.3 Structural Similarity Searching

Structural similarity searching employs molecular fingerprints and descriptors to identify compounds similar to known bioactive molecules. This approach is particularly valuable when limited structural information is available about the target. Similarity searching can rapidly screen large databases to identify compounds with structural features associated with biological activity.

The integration of multiple ligand-based approaches, including pharmacophore modeling, QSAR, and similarity searching, provides complementary information that enhances the reliability of virtual screening predictions. The combination of these approaches with structure-based methods offers a comprehensive strategy for natural product drug discovery.

Table 2: Comparison of Ligand-Based Virtual Screening Approaches

Approach	Principle	Data Required	Strengths	Limitations
Pharmacophore Modeling	3D feature arrangement	Active compounds or target structure	3D information, interpretable	Quality of pharmacophore critical
QSAR	Structure-activity correlation	Active and inactive compounds	Predictive, quantitative	Requires training data
Similarity Searching	Molecular similarity	Known active compounds	Rapid, simple	Dependent on query compound
3D-QSAR (CoMFA/CoMSIA)	3D field analysis	Aligned active compounds	3D information, interpretable	Alignment-dependent

4 MOLECULAR DYNAMICS SIMULATIONS

4.1 Principles and Applications

Molecular dynamics (MD) simulations provide atomic-level insights into the dynamic behavior of protein-ligand complexes, complementing the static picture provided by molecular docking. MD simulations enable the exploration of conformational changes, the assessment of binding stability, and the calculation of more accurate binding free energies.

The application of molecular dynamics simulations in natural product drug discovery has gained significant traction. MD simulations can refine docking poses, identify stable binding conformations, and provide insights into the molecular mechanisms of ligand binding. The integration of MD with docking and other computational approaches enhances the reliability of predictions.

4.2 Free Energy Calculations

Free energy calculations, including MM-GBSA and MM-PBSA, provide more accurate estimates of binding affinities than empirical scoring functions. These methods combine molecular mechanics with continuum solvation models to calculate the free energy of binding. While computationally intensive, free energy calculations offer improved accuracy for lead optimization and compound prioritization.

The application of free energy calculations to natural product libraries enables the identification of compounds with favorable binding thermodynamics, guiding the selection of candidates for experimental validation. The integration of these calculations with other computational approaches enhances the efficiency of natural product drug discovery.

5 ADMET PREDICTION AND PHARMACOKINETIC PROFILING

5.1 Importance of Early-Stage ADMET Assessment

Early-stage ADME-Tox analysis of phytocompounds aids the discovery of potent drugs (From roots to codes, 2023). The pharmacokinetic and ADMET profiling of plant-based therapeutics is essential for drug development (From roots to codes, 2023). Computational prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties enables the early identification of compounds with unfavorable pharmacokinetic profiles, reducing attrition in later stages of development.

Computational approaches such as ADMET prediction have been applied in natural products-based drug discovery, enabling the selection of compounds with auspicious pharmacokinetic and pharmacodynamic profiles (Computational Pharmacology and In Silico Clinical Trials, 2023). This approach minimizes the attrition rate in later clinical stages, as the most promising compounds are chosen for further development.

5.2 Available Tools and Databases

Several databases and webservers are available in the public domain for phytocompound-related information that can be harnessed for drug discovery (Recent advances in plant-based anti-cancer drug discovery, 2023). These resources include natural product databases, ADMET prediction tools, and computational platforms for virtual screening.

The most commonly used databases and computational tools include TCMSP for traditional Chinese medicine compounds, AutoDock Vina for molecular docking, and GROMACS for molecular dynamics simulations (A review on computational approaches, 2022). The availability of these resources has democratized computational drug discovery, enabling researchers worldwide to apply CADD approaches to natural product research.

5.3 Integration with Virtual Screening

The integration of ADMET prediction with virtual screening enables the identification of compounds that not only bind to the target but also possess favorable pharmacokinetic properties. This integrated approach reduces the risk of late-stage failures due to poor bioavailability, toxicity, or rapid clearance. The application of ADMET filters to virtual screening hits prioritizes compounds with the greatest potential for successful clinical development.

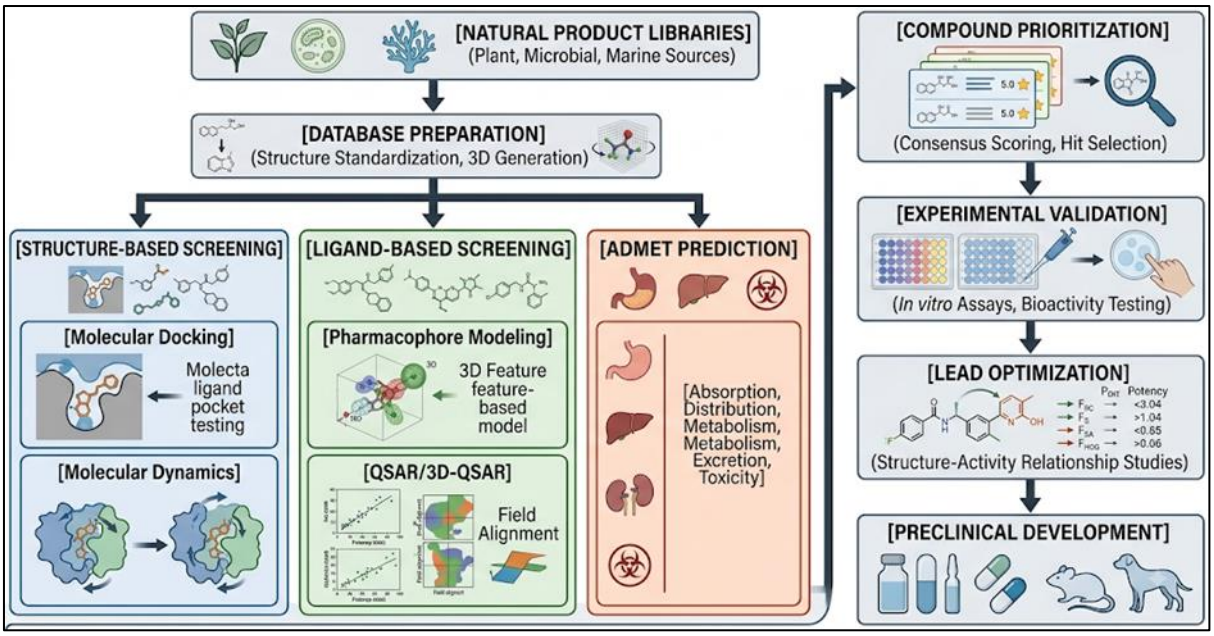

Figure 1: Computer-Aided Natural Product Drug Discovery Workflow

6 INTEGRATIVE AND EMERGING APPROACHES

6.1 Machine Learning and Artificial Intelligence

The integration of advanced Machine Learning and Artificial Intelligence approaches could alleviate the challenges faced by traditional computational techniques, thus enriching the screening process (From roots to codes, 2023). Developments in computational omics technologies have provided new means to access the hidden diversity of natural products, unearthing new potential for drug discovery (Mullowney et al., 2023).

Artificial intelligence for natural product drug discovery has emerged as a transformative approach, with machine learning models enhancing the prediction of bioactivity, toxicity, and pharmacokinetic properties (Mullowney et al., 2023). The synergy between machine learning and natural products cheminformatics has been applied to lead discovery, demonstrating the potential of these approaches to accelerate natural product-based drug discovery (Synergy between machine learning and natural products cheminformatics, 2022).

High-throughput virtual screening and their strategies, and significance, have been reviewed in the context of natural products, highlighting the role of computational approaches in navigating natural product chemical space (Synergy between machine learning and natural products cheminformatics, 2022).

6.2 Network Pharmacology

Network pharmacology represents an emerging approach that integrates computational and systems biology to understand the multi-target effects of natural products. Traditional computational approaches as well as newer techniques like network pharmacology and machine learning have been applied to identify phytomolecules as leads against cancer (Recent advances in plant-based anti-cancer drug discovery, 2023).

Network pharmacology enables the identification of compounds that modulate multiple targets within disease-relevant pathways, reflecting the polypharmacological nature of many natural products. This approach is particularly valuable for natural products, which often exert their therapeutic effects through interactions with multiple targets.

6.3 Combined In-Silico and In-Vitro Studies

Combined in-silico and in-vitro studies can validate the drug discovery results (From roots to codes, 2023). The corroborative in-silico and experimental approaches to identify potential therapeutics from medicinal plants have been highlighted (From roots to codes, 2023). This integrated approach leverages the efficiency of computational screening while confirming predictions through rigorous experimental testing.

The integration of computational and experimental approaches has rendered the use of in silico-based approaches even more popular and successful in the investigation of natural products (Simoben et al., 2023). The combination has

enabled researchers to overcome the limitations of each approach individually, accelerating the discovery and development of natural product-based therapeutics.

7 CHALLENGES AND LIMITATIONS

7.1 Scoring Function Accuracy

The accuracy of scoring functions is a major limitation in molecular docking. Scoring functions trained on synthetic compounds may not accurately predict natural product binding. The development of scoring functions specifically for natural products is needed. The unique physicochemical properties of natural products, including their often larger size and greater complexity, present challenges for current scoring functions.

7.2 Conformational Flexibility

The conformational flexibility of natural products presents computational challenges. The exploration of conformational space for large, flexible molecules is computationally intensive. Enhanced sampling methods may improve conformational exploration. The presence of multiple rotatable bonds and stereocenters significantly increases the complexity of conformational searching.

7.3 Stereochemical Complexity

Natural products often contain multiple stereocenters, requiring consideration of stereoisomers. Different stereoisomers may have different biological activities. The computational treatment of stereoisomers is challenging but essential. The representation of stereochemistry in natural product databases and the consideration of stereoisomers in virtual screening remain significant challenges.

7.4 Data Availability and Quality

Identifying and proposing novel natural product-based hits for experimental validation comes with several challenges such as the availability of compounds by suppliers, the huge task of separating pure compounds from complex mixtures, the quantity of samples available from the natural source to be tested, not to mention the potential ecological impact if the natural source is exhausted (Simoben et al., 2023). The limited availability of high-quality, standardized natural product data constrains model development and validation.

7.5 Experimental Validation

The translation of computational predictions to experimental validation remains a significant challenge. The gap between in silico predictions and in vitro/in vivo outcomes requires careful consideration. The development of robust experimental validation protocols and the integration of computational and experimental approaches are essential for successful natural product drug discovery.

8 FUTURE PERSPECTIVES

The future of computer-aided natural product drug discovery lies in the integration of emerging technologies and innovative approaches. The application of artificial intelligence and deep learning will enhance predictive capabilities and enable the exploration of previously inaccessible chemical space. The development of scoring functions specifically for natural products will improve docking accuracy. The integration of multi-omics data will provide comprehensive biological context for natural product activity. The development of integrated computational-experimental platforms will accelerate discovery.

The application of generative models for natural product-like molecule design represents a promising frontier. The integration of network pharmacology and systems biology approaches will enable the identification of multi-target natural products with enhanced therapeutic potential. The development of comprehensive natural product databases and the application of machine learning to these resources will accelerate hit identification and lead optimization.

Continued investment in natural product databases, computational resources, and interdisciplinary collaboration is essential for advancing the field. The integration of computational approaches with traditional natural product discovery methods promises to accelerate the identification and development of novel therapeutics from natural sources.

9 CONCLUSION

Computer-aided drug discovery has emerged as an essential tool in natural product research, enabling the efficient identification and optimization of bioactive compounds. Structure-based approaches, including molecular docking and molecular dynamics, enable the prediction of binding modes and affinities based on target protein structures. Ligand-based approaches, including pharmacophore modeling and QSAR, enable the identification of bioactive compounds based on known active molecules. The integration of ADMET prediction with virtual screening enables the identification of compounds with favorable pharmacokinetic properties. The application of machine learning and artificial intelligence approaches promises to enhance predictive capabilities and accelerate natural product drug discovery. Despite significant advances, challenges including scoring function accuracy, conformational flexibility, stereochemical complexity, and experimental validation persist. The continued development of computational methodologies, databases, and integrated approaches is essential for realizing the full potential of CADD in natural product drug discovery.

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