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Integrated Computational Approaches for Natural Product-Based Drug Discovery: Target Prediction, Network Pharmacology, Molecular Docking, and ADMET Prediction

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A B S T R A C T

Natural products remain an important source of drug discovery, while advances in computational approaches have accelerated early-stage candidate identification. This review aims to provide an integrated overview of target prediction, network pharmacology, molecular docking, and ADMET prediction within a unified computational workflow for natural product-based drug discovery. A narrative literature review was conducted by analyzing peer-reviewed articles published between 2015 and 2025 from major scientific databases. The reviewed studies consistently demonstrate that integrating complementary *in silico* approaches improves target identification, mechanism elucidation, lead compound prioritization, and pharmacokinetic assessment before experimental validation. This integrated workflow provides a practical framework to support more efficient, systematic, and evidence-based natural product-driven drug discovery.

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INTRODUCTION

Natural products have long been recognized as an important source of bioactive compounds for drug discovery due to their remarkable structural diversity and broad range of biological activities. Numerous therapeutic agents have been developed from natural compounds or their derivatives, demonstrating their significant contribution to the treatment of various diseases, including cancer, infectious diseases, and inflammatory disorders. Consequently, natural products continue to attract considerable attention as promising sources of novel drug candidates (Atanasov et al., 2021; Newman & Cragg, 2020).

Despite their therapeutic potential, the discovery and development of natural product-derived drugs remain challenging because conventional approaches require extensive laboratory screening, target identification, and pharmacological evaluation, which are often time-consuming and costly. Recent advances in computational biology and bioinformatics have accelerated this process by enabling rapid *in silico* analyses, including the identification of biological targets, prediction of ligand–protein interactions, and evaluation of pharmacokinetic and toxicity profiles before experimental validation (Romano & Tatonetti, 2019; Sadybekov & Katritch, 2023).

Among the available computational approaches, target prediction, network pharmacology, molecular docking, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction have become the most widely applied methods in natural product research. These approaches are increasingly implemented as an integrated workflow, where the output of one stage serves as the basis for the next, providing a more comprehensive understanding of the pharmacological mechanisms and drug potential of bioactive compounds (Hopkins, 2008; Simoben et al., 2023).

Although numerous review articles have discussed individual computational methods, their integration into a unified computational workflow for natural product-based drug discovery has received comparatively less attention. Therefore, this review summarizes recent advances in target prediction, network pharmacology, molecular docking, and ADMET prediction, while emphasizing how these complementary approaches can be integrated into a systematic computational workflow for the identification and prioritization of promising natural product-derived drug candidates.

THEORETICAL REVIEW

Computational drug discovery has become an important component of modern natural product research by integrating computational biology, cheminformatics, and bioinformatics to support the identification of promising drug candidates. Compared with conventional experimental approaches, computational methods enable rapid screening of bioactive compounds, prediction of biological targets, evaluation of ligand–protein interactions, and estimation of pharmacokinetic properties, thereby reducing both research time and development costs (Romano & Tatonetti, 2019; Sadybekov & Katritch, 2023).

In natural product research, the integration of target prediction, network pharmacology, molecular docking, and ADMET prediction provides

complementary information throughout the drug discovery process. This integrated workflow facilitates a more comprehensive understanding of the therapeutic potential of natural compounds before experimental validation (Atanasov et al., 2021; Simoben et al., 2023)

METHODOLOGY

This study employed a narrative literature review approach to synthesize current evidence regarding integrated computational approaches in natural product-based drug discovery. Relevant articles were retrieved from Scopus, Web of Science, PubMed, and Google Scholar using combinations of the keywords natural products, computational drug discovery, target prediction, network pharmacology, molecular docking, and ADMET prediction.

Peer-reviewed publications published between 2015 and 2025 were prioritized. The selected literature was screened based on relevance to the objectives of this review and then analyzed thematically to describe the application, integration, challenges, and future perspectives of computational approaches in natural product-based drug discovery.

RESULTS

Integrated Computational Workflow

Integrated computational approaches have become an essential workflow in natural product-based drug discovery. This workflow typically integrates target prediction, network pharmacology, molecular docking, and ADMET prediction prior to experimental validation.

Table 1. Summary of integrated computational approaches

Authors	Computational Approaches	Main Findings
(Chen et al., 2017)	Target prediction, Docking	Computational methods improve drug discovery efficiency
(Newman & Cragg, 2020)	Drug discovery overview	Natural products remain an important source of new drugs
(Atanasov et al., 2021)	Integrated computational approaches	Computational methods accelerate natural product research
(Sadybekov & Katritch, 2023)	AI-assisted drug discovery	Integrated workflow supports early-stage drug discovery
(Simoben et al., 2023)	Docking, ADMET	*In silico* approaches improve candidate prioritization

The studies summarized in Table 1 demonstrate that integrated computational approaches follow a systematic workflow in which each computational method contributes complementary information during the drug discovery process. Based on the synthesis of the reviewed literature, the overall computational workflow is illustrated in Figure 1.

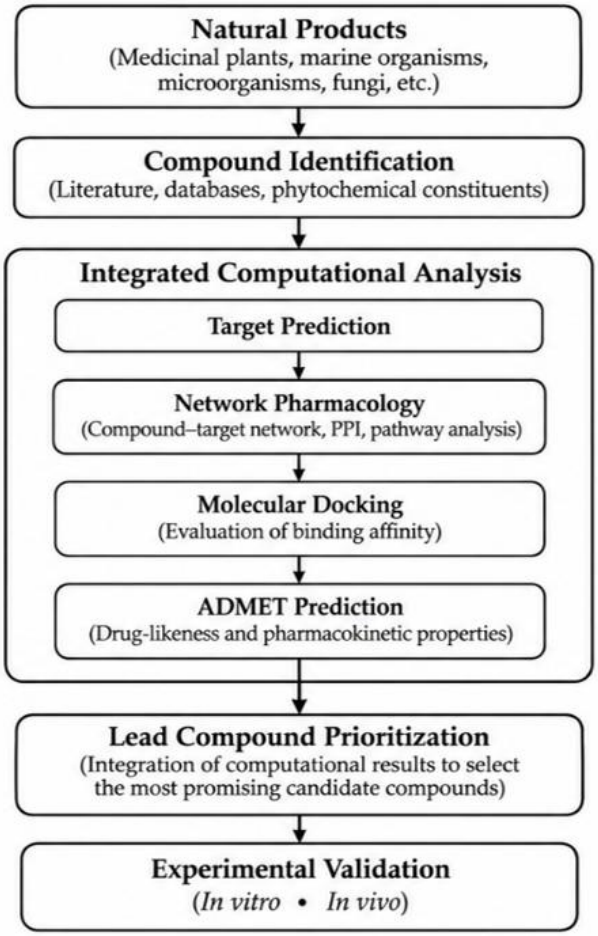

Figure 1. Integrated computational workflow for natural product-based drug discovery

Figure 1 illustrates the sequential integration of target prediction, network pharmacology, molecular docking, and ADMET prediction for prioritizing promising natural compounds before experimental validation. This workflow provides a general framework adopted in many recent studies and serves as the basis for the subsequent discussion of each computational approach in this review.

Target Prediction

Target prediction is commonly used to identify potential protein targets associated with bioactive compounds before further computational analyses are performed. Various web-based platforms have been developed to predict compound–target interactions using chemical similarity, pharmacophore mapping, and machine learning algorithms.

Table 2. Target prediction studies

Authors	Platform	Main Findings
(Gfeller et al., 2014)	SwissTarget Prediction	Predicts protein targets based on chemical similarity
(Liu et al., 2016)	BATMAN-TCM	Identifies targets and pathways for herbal compounds
(Daina et al., 2017)	SwissTarget Prediction	Improved prediction accuracy for small molecules
(Simoben et al., 2023)	Multiple platforms	Target prediction supports multitarget drug discovery

Network Pharmacology

Network pharmacology has become an important approach for understanding the multitarget mechanisms of natural compounds through biological network analysis. This approach integrates compound–target interactions with protein–protein interaction networks and pathway enrichment analyses to identify key therapeutic targets.

Table 3. Network pharmacology studies

Authors	Analysis	Main Findings
(Hopkins, 2008)	Network pharmacology	Introduced the network-based drug discovery concept
(Ru et al., 2014)	TCMSP	Integrates compounds, targets, and pathways
(Szklarczyk et al., 2023)	STRING	Identifies protein interaction networks
(Noor et al., 2022)	GO–KEGG	Summarizes pathway enrichment analysis for elucidating biological mechanisms of medicinal plants

Molecular Docking

Molecular docking is widely employed to evaluate ligand–protein interactions and estimate binding affinity between natural compounds and target proteins. It is frequently used to validate target prediction and support the identification of promising lead compounds.

Table 4. Molecular docking studies

Authors	Software	Main Findings
(Meng et al., 2011)	AutoDock	Docking predicts ligand–protein interactions
(Pagadala et al., 2017)	AutoDock, Glide	Review of docking software
(Pinzi & Rastelli, 2019)	Multiple software	Recent advances in docking applications
(Simoben et al., 2023)	Docking workflow	Docking supports natural product screening

ADMET Prediction

ADMET prediction is increasingly incorporated into computational drug discovery to estimate pharmacokinetic properties and toxicity profiles before experimental studies. Early evaluation of drug-likeness facilitates the prioritization of compounds with favorable pharmacological characteristics.

Table 5. ADMET prediction studies

Authors	Platform	Main Findings
(Daina et al., 2017)	SwissADME	Predicts pharmacokinetic properties and drug-likeness
(Pires et al., 2015)	pkCSM	Predicts ADMET using graph-based signatures
(Yang et al., 2019)	admetSAR 2.0	Comprehensive ADMET prediction platform
(Simoben et al., 2023)	Multiple tools	ADMET supports lead compound selection

DISCUSSION

The findings of this review indicate that computational drug discovery has evolved from the application of individual *in silico* methods toward an integrated workflow, as illustrated in Figure 1. The combination of target prediction, network pharmacology, molecular docking, and ADMET prediction provides complementary information for identifying biological targets, elucidating molecular mechanisms, evaluating ligand–protein interactions, and assessing pharmacokinetic properties prior to experimental validation. Such integration has significantly improved the efficiency of natural product-based drug discovery while reducing the time and cost associated with conventional screening approaches (Nogales et al., 2022; Paul et al., 2021; Sadybekov & Katritch, 2023).

The review also highlights that each computational approach contributes different but interconnected information throughout the drug discovery pipeline. As shown in Figure 1, these computational approaches are integrated into a sequential workflow that supports lead compound prioritization before experimental validation. Target prediction identifies potential molecular targets, network pharmacology explains the relationships among compounds, targets, and biological pathways, molecular docking validates ligand–protein interactions, whereas ADMET prediction evaluates drug-likeness and pharmacokinetic characteristics. Therefore, these methods should not be considered independent techniques but rather complementary tools that collectively improve the prioritization of lead compounds (Atanasov et al., 2021; Noor et al., 2022; Simoben et al., 2023).

Table 6. Comparison of integrated computational approaches

Approach	Main Strengths	Limitations	Typical Applications
Target Prediction	Rapid identification of potential protein targets	Prediction accuracy depends on available databases and algorithms	Target identification and prioritization
Network Pharmacology	Explores multi-target and multi-pathway mechanisms	Results are highly dependent on database completeness	Mechanism of action and pathway analysis
Molecular Docking	Evaluates ligand–protein interactions and binding affinity	Represents static interactions and cannot fully describe molecular dynamics	Binding validation and lead compound selection
ADMET Prediction	Early evaluation of pharmacokinetic and toxicity profiles	Computational prediction requires experimental confirmation	Drug-likeness assessment and compound prioritization

The comparison presented in Table 6 further supports the integrated workflow illustrated in Figure 1, demonstrating that no single computational method is sufficient to support the entire drug discovery process. Instead, integrating these approaches provides more comprehensive evidence for selecting promising natural compounds and understanding their biological mechanisms. This integrated workflow has therefore become the preferred strategy in contemporary computational drug discovery, particularly for natural products

with multi-component and multi-target characteristics (Jumper et al., 2021; Varadi et al., 2022).

Despite these advantages, several challenges remain. Prediction accuracy is influenced by the quality of chemical and biological databases, while differences among computational algorithms may produce inconsistent results. Moreover, computational analyses cannot fully replicate the complexity of biological systems; therefore, experimental validation remains essential to confirm the predicted therapeutic potential of natural compounds (Chen et al., 2017; Hollingsworth & Dror, 2018).

Future developments are expected to integrate artificial intelligence (AI), multi-omics data, and molecular dynamics simulations into computational drug discovery. Recent advances in AI, particularly machine learning and deep learning, have shown considerable potential to improve target prediction, virtual screening, and ADMET prediction by enabling the analysis of increasingly complex biological datasets. In addition, continuous improvements in public databases and predictive algorithms are anticipated to enhance the reliability of target identification, interaction analysis, and pharmacokinetic prediction, thereby accelerating the discovery and development of natural product-derived therapeutic agents (Paul et al., 2021; Sadybekov & Katritch, 2023; Varadi et al., 2022).

CONCLUSIONS AND RECOMMENDATIONS

This review demonstrates that integrated computational approaches have become an effective strategy for accelerating natural product-based drug discovery. The integration of target prediction, network pharmacology, molecular docking, and ADMET prediction provides complementary information for identifying biological targets, elucidating molecular mechanisms, evaluating ligand–protein interactions, and assessing pharmacokinetic properties before experimental validation. Consequently, these approaches improve the efficiency of candidate selection while reducing the time and cost associated with conventional drug discovery.

The findings also indicate that no single computational approach is sufficient to comprehensively evaluate the therapeutic potential of natural products. Instead, integrating multiple computational methods offers a more systematic and reliable workflow for prioritizing bioactive compounds and supporting subsequent experimental studies. Therefore, integrated computational approaches have become an essential component of modern natural product-based drug discovery. The workflow synthesized in this review provides a practical framework that may guide future studies in selecting and prioritizing bioactive natural compounds before experimental validation.

Recommendations

Future studies should emphasize the integration of computational approaches with experimental validation to improve the reliability and translational value of drug discovery research. In addition, advances in artificial intelligence, multi-omics technologies, and continuously expanding biological databases are expected to further enhance the accuracy, efficiency, and

applicability of computational methods in discovering novel bioactive compounds from natural products.

FURTHER STUDY

This review has several limitations. First, the discussion was limited to four major computational approaches, namely target prediction, network pharmacology, molecular docking, and ADMET prediction, while other emerging techniques such as molecular dynamics simulations, machine learning, and multi-omics integration were not discussed in detail. Second, this review synthesized findings from published literature without performing experimental validation or quantitative meta-analysis.

Future studies are encouraged to integrate additional computational methods with experimental validation to improve the reliability of natural product-based drug discovery. Furthermore, comprehensive evaluations involving artificial intelligence, molecular dynamics simulations, and multi-omics analyses may provide deeper insights into the pharmacological mechanisms and therapeutic potential of natural bioactive compounds.

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