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Review

Computational Approaches in Natural Product Drug Discovery and Development

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Abstract: Natural products remain a major source of new therapeutic agents, and many clinically important drugs originate from bioactive scaffolds refined through modern chemistry. Traditional discovery approaches rely on empirical knowledge and labour-intensive extraction, and they face challenges such as variability in source materials, limited standardisation, and ethical considerations. Advances in computational science now create new opportunities for discovery and development. Cheminformatics, artificial intelligence, and network pharmacology provide rapid screening, predictive modelling, and mechanistic interpretation. The integration of genomics, transcriptomics, proteomics, and metabolomics creates a systems-level perspective on biosynthetic pathways and molecular complexity. This perspective strengthens analytical accuracy, reduces material requirements, and supports sustainable innovation. This review describes the evolution of natural-product drug discovery in the computational era and highlights the role of digital technologies in modern product development.

Keywords: natural-product drug discovery; computational pharmacology; cheminformatics; artificial intelligence; network pharmacology; digital technologies

1. Introduction

Natural products remain central to drug discovery and continue to provide structurally diverse compounds with therapeutic relevance. Their chemical diversity reflects millions of years of evolutionary selection, producing metabolites that interact with defined molecular targets and influence complex biological pathways [1–3]. Many clinically important drugs originate from natural scaffolds refined through medicinal chemistry to improve potency, selectivity, and pharmacokinetic behaviour [3]. Traditional medical systems, including Traditional Chinese Medicine and other regional ethnotherapies, document the use of thousands of species and continue to guide modern research [4]. These systems highlight the therapeutic potential of multi-component preparations, where coordinated modulation of several pathways aligns with the polygenic nature of chronic diseases [5]. The complexity of these systems increasingly requires computational approaches capable of interpreting multi-layered chemical and biological information.

1.1. Limitations of Traditional Discovery Approaches

Traditional discovery methods face persistent challenges. Chemical variability in biological material, seasonal and geographical influences, and labour-intensive extraction and isolation limit reproducibility and scalability. Sustainable sourcing remains a concern, particularly for species threatened by overharvesting or habitat loss. Ethical issues such as inadequate benefit-sharing further complicate development and emphasise the need for transparent frameworks [5]. These constraints highlight the limitations of empirical discovery and underscore the value of computational tools that provide reproducible, scalable, and mechanism-driven alternatives.

1.2. Computational Acceleration of Natural-Product Research

Advances in cheminformatics, artificial intelligence, and network pharmacology now support rapid screening of large natural-product libraries, prediction of compound-target interactions, and early assessment of pharmacokinetic and safety profiles [6–10]. Network-based approaches provide mechanistic insight into multi-component therapeutics and help identify synergistic interactions that emerge from complex mixtures [11,12]. Virtual screening, molecular docking, and scoring algorithms enable rapid prioritisation of bioactive candidates and guide structure-based optimisation [13]. Machine-learning-driven prediction platforms support toxicity assessment, ADMET profiling, and target identification [14,15]. Artificial intelligence further accelerates hypothesis generation, literature-based discovery, and the integration of heterogeneous datasets [16–22]. Overall, these tools form the foundation of predictive discovery pipelines that increasingly guide early-stage decision-making.

1.3. Multi-Omics Integration and the Emergence of Predictive Pipelines

Multi-omics platforms, including genomics, transcriptomics, proteomics, and metabolomics, provide a systems-level view of biosynthetic pathways and link chemical diversity to genetic and environmental factors [21,22]. These approaches strengthen authentication, guide metabolic engineering, and support the discovery of rare or low-abundance metabolites. Databases such as IMPPAT and ADMETlab integrate phytochemical, pharmacological, and computational information, enabling reproducible and scalable workflows for natural-product research [14,15]. Modern natural-product discovery increasingly depends on integrated computational and multi-omics strategies that unify chemical, biological, and pharmacokinetic data into predictive pipelines [20]. The convergence of computational and experimental methodologies creates a mechanism-driven framework that accelerates the transition from traditional knowledge to industrial application [19,20]. Figure 1 outlines the conceptual architecture that shapes contemporary natural-product drug discovery.

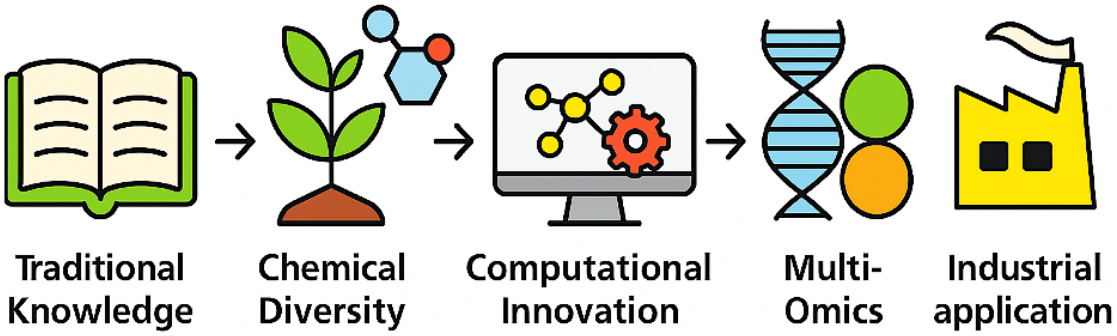

Figure 1. Conceptual framework for modern natural-product drug discovery.

Traditional knowledge provides the initial therapeutic context and guides species selection [1,4]. Chemical diversity reflects specialised biosynthetic pathways that generate structurally complex metabolites with defined biological activity [2,3]. Limitations of traditional methods highlight the need for reproducible, scalable, and sustainable workflows [5]. Computational innovation introduces predictive tools that support rapid screening, target identification, and early optimisation [6–10]. Multi-omics platforms link genetic, metabolic, and proteomic information to biosynthetic capacity and chemical profiles [17,18]. Industrial relevance emerges from the convergence of these domains, enabling mechanism-driven development of reproducible and high-value natural-product-based therapeutics [19,20]. This integration also aligns discovery with industrial requirements for standardisation, sustainability, and scalable production.

1.4. Scope of This Review

This review examines how computational tools support natural-product drug discovery and development. It outlines how digital methods integrate with analytical science to strengthen lead identification, clarify mechanisms, and support sustainable production. The review also considers the industrial implications of these advances and the opportunities they create for next-generation natural-product therapeutics. Although computational approaches to natural-product research have been reviewed previously, these publications typically examine cheminformatics, artificial intelligence, network pharmacology, or multi-omics as separate domains [10,12,17,18,21–24]. This review

differs by synthesising these domains into a unified, predictive, and industrially aligned pipeline that reflects contemporary development strategies. This review highlights practical significance by connecting recent computational developments with biosynthetic engineering, sustainability, and industrial scalability. It offers a unified viewpoint that previous reviews [25–27] have not provided.

2. Challenges in Traditional Natural-Product Drug Discovery

Traditional natural-product drug discovery relies on empirical knowledge, historical use, and labour-intensive laboratory workflows. These approaches have produced many important therapeutics, yet they face persistent limitations that restrict reproducibility, scalability, and industrial translation. Variability in biological material remains a major challenge. Species identity, geographical origin, soil composition, climate, and harvesting practices influence the concentration and distribution of bioactive metabolites [8,9]. Seasonal changes alter biosynthetic pathways, and post-harvest handling affects chemical stability. Such fluctuations complicate standardisation and weaken the reliability of pharmacological outcomes, particularly when moving from small-scale studies to industrial production.

2.1. Extraction, Isolation, and Resource Constraints

Extraction and isolation processes are often slow and resource-intensive. Large quantities of raw material are required to obtain small amounts of active compounds, particularly when metabolites occur at low abundance [3]. Fractionation and purification demand repeated chromatographic steps, and dereplication is essential to avoid re-isolating known compounds. These workflows consume time, solvents, and analytical capacity, increasing the cost of development. Discovery efforts are further constrained when promising metabolites originate from rare, slow-growing, or endangered species, raising both practical and sustainability concerns [9].

2.2. Ethical, Regulatory, and Methodological Limitations

Ethical and regulatory issues add further complexity. Biopiracy, inadequate benefit-sharing, and unclear intellectual-property frameworks create barriers to equitable development and international collaboration [10]. Many traditional preparations involve multiple constituents, yet their complexity challenges conventional pharmacological evaluation. Synergistic interactions may contribute to therapeutic effects, but they are difficult to isolate and validate using classical reductionist methods [7]. The gap between traditional formulations and modern regulatory expectations underscores the need for approaches that can interpret multi-component systems without oversimplifying them.

2.3. Computational Solutions to Traditional Constraints

Computational methodologies address many of these challenges by reducing material use, guiding experimental design, and improving mechanistic understanding. Predictive models identify promising scaffolds before extraction, and cheminformatics filters reduce redundancy by highlighting structural novelty [11]. Network-based approaches reveal multi-target interactions that align with the complexity of chronic diseases [12]. Multi-omics platforms link chemical diversity to genetic and environmental factors, improving authentication and supporting sustainable sourcing [14,15]. Together, these tools shift discovery from empirical exploration to mechanism-driven prioritisation, creating workflows that are more efficient, reproducible, and aligned with industrial needs. Figure 2 depicts the major constraints that limit traditional natural-product drug discovery and shows how computational methodologies address these barriers.

Variability in biological material arises from environmental, seasonal, and geographical influences that alter metabolite profiles and complicate standardisation [8,14]. Extraction and isolation remain labour-intensive and require large quantities of raw material, particularly when active compounds occur at low abundance [3]. Multi-component preparations introduce synergistic interactions that are difficult to isolate using classical reductionist methods [7]. Ethical and sustainability concerns, including overharvesting and inadequate benefit-sharing, further restrict development [9,10]. Computational tools provide solutions by predicting promising scaffolds before extraction, mapping compound-target-pathway relationships, linking chemical diversity to biosynthetic pathways, and supporting traceability and compliance [11–15]. The integration of these digital approaches transforms traditional workflows into predictive, scalable, and sustainability-aligned discovery pipelines.

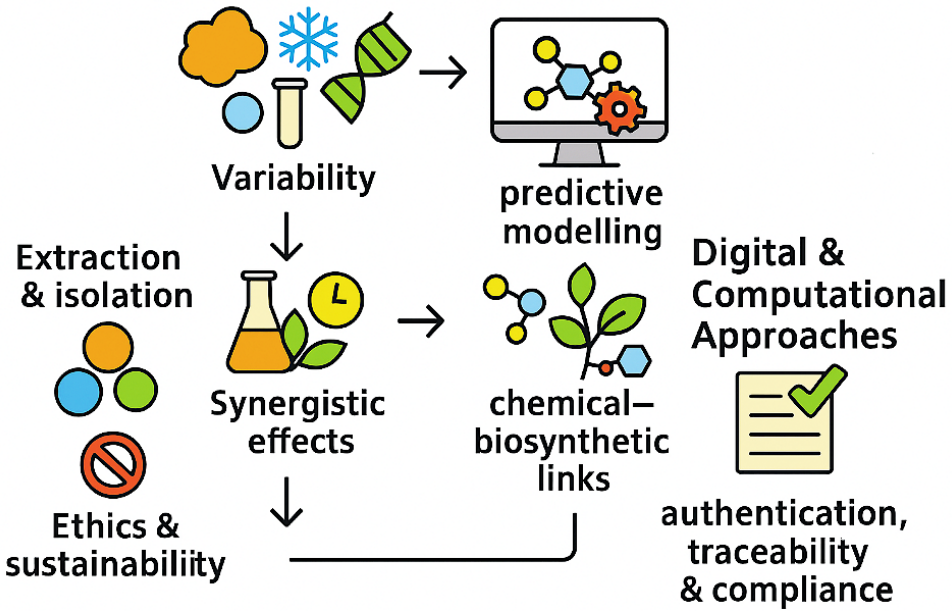

Figure 2. Challenges in traditional natural-product drug discovery and the role of computational tools.

3. Computational Foundations of Modern Natural-Product Drug Discovery

Computational science now anchors contemporary natural product drug discovery by enabling rapid, predictive, and mechanism-oriented analysis of structurally diverse metabolites. These methods reduce dependence on extensive extraction, improve early decision-making, and create reproducible workflows that meet industrial expectations for efficiency, scalability, and regulatory alignment. The field has moved from isolated computational tools toward integrated digital ecosystems that connect chemical structure, biological function, and biosynthetic context [20]. The combined use of cheminformatics, artificial intelligence, network pharmacology, and multi-omics has shifted discovery from empirical screening to a data-centred, hypothesis-driven framework [11–15].

3.1. Cheminformatics: Digital Representation and Early Filtering

Cheminformatics converts natural-product structures into computational formats that allow systematic evaluation of physicochemical properties, drug-likeness, and structural novelty. Similarity metrics, descriptor-based filters, and dereplication tools highlight promising scaffolds before laboratory extraction, reducing redundancy and preventing the re-isolation of known compounds [11]. Docking-based prediction of binding affinity and interaction patterns provides early mechanistic hypotheses and helps prioritise compounds with favourable ADMET characteristics. These digital filters act as the first gatekeepers in modern discovery pipelines, ensuring that experimental resources are directed toward the most promising chemical space.

3.2. Artificial Intelligence: Predictive Modelling and Analogue Design

Artificial intelligence (AI) expands these capabilities by learning from large chemical and biological datasets. Machine-learning models classify bioactivity, predict compound-target interactions, and estimate toxicity with increasing accuracy [20–22]. Deep-learning architectures recognise structural features that conventional descriptors may overlook, while generative and reinforcement-learning models design new analogues inspired by natural scaffolds and optimise them for potency, selectivity, and safety [21]. AI therefore functions not only as a predictive engine but also as a creative tool, proposing structural innovations that extend beyond known natural product space and accelerating hit-to-lead progression.

3.3. Network Pharmacology: Systems-Level Mechanistic Insight

Network pharmacology offers a complementary system-level perspective. Many natural product compounds act on multiple targets, and multi-component preparations influence several pathways simultaneously. Network-based models map these interactions and reveal how combinations of metabolites modulate disease-relevant signalling cascades [6,7]. This approach aligns with the complexity of chronic diseases, where coordinated modulation of multiple pathways may be more effective than single-target strategies. By identifying convergence

points, network analysis clarifies why certain traditional formulations exhibit robust therapeutic effects and guides rational formulation design.

3.4. Multi-Omics Integration: Linking Genetics, Chemistry, and Environment

Multi-omics integration links chemical diversity to biosynthetic capacity and environmental influence. Genomics identifies gene clusters responsible for secondary-metabolite production, while transcriptomics and proteomics reveal regulatory responses and enzymatic machinery [14,15]. Metabolomics provides a direct chemical fingerprint of biological material, supporting authentication, quality control, and sustainability. When combined with computational modelling, multi-omics platforms guide metabolic engineering, improve yields of rare metabolites, and uncover new biosynthetic pathways. This integration transforms natural product research from a chemistry-driven discipline into a systems-level science capable of predicting how genetics, environment, and metabolism shape chemical output. Figure 3 summarises the computational foundations of modern natural product drug discovery.

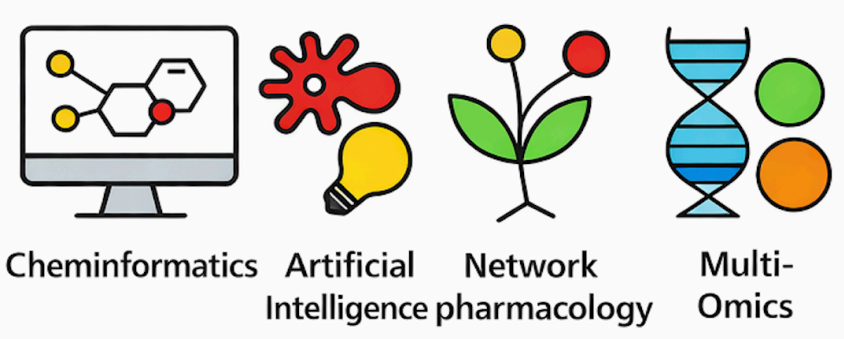

Figure 3. Computational foundations of modern natural-product drug discovery.

Cheminformatics provides structural insight, artificial intelligence predicts biological activity, network pharmacology maps multi-target interactions, and multi-omics links genetic and chemical diversity.

4. Cheminformatics and Virtual Screening in Natural Product Drug Discovery

Cheminformatics provides structural representation and early filtering of phytochemicals, while artificial intelligence predicts compound-target interactions, optimises pharmacokinetic properties, and designs new analogues [20,21]. Network pharmacology maps multi-target and multi-pathway interactions relevant to complex diseases [6]. Multi-omics platforms link genetic, proteomic, and metabolic information to biosynthetic pathways and chemical diversity [14]. In addition, these approaches form a digitally coordinated discovery pipeline that replaces broad empirical screening with targeted, mechanism-driven prioritisation [22].

4.1. Foundations of Cheminformatics in Natural Product Research

Cheminformatics enables the digital representation of phytochemicals, supports rapid screening of large compound libraries, and reduces reliance on labour-intensive experimental workflows. Traditional discovery depends on biochemical assays, high-throughput screening, and iterative optimisation, but these approaches require extensive resources and often yield low success rates. Only a small fraction of screened compounds progress to clinical evaluation, and many fail due to inadequate efficacy, toxicity, or unfavourable pharmacokinetic behaviour [28,29]. Computational tools address these limitations by improving early prediction and reducing experimental burden [11]. Applications across natural-product research illustrate how digital filtering reshapes early discovery. Pharmacophore-based virtual screening has prioritised camptothecin analogues with improved topoisomerase-I inhibition, reducing the need for extensive extraction from *Camptotheca acuminata* [23,30]. Descriptor-based clustering has also been used to identify structurally novel limonoids and guide targeted isolation, preventing redundancy and improving early decision-making in natural-product pipelines [10,12,24].

4.2. Target Identification and Druggability Prediction

Target identification is a critical first step in drug discovery, yet it remains one of the most time-consuming phases. Conventional methods rely on cellular assays, genomic studies, and biochemical validation, but these processes require significant time and specialised expertise [31]. Cheminformatics accelerates this stage by

analysing structural features, predicting druggability, and identifying molecular interactions that align with disease-relevant pathways [32]. These tools also support the identification of hit molecules by enabling virtual screening of millions of compounds before laboratory testing, reducing the need for large-scale experimental assays [33,34]. Ensemble machine-learning frameworks have expanded this capability by identifying previously unrecognised protein targets for natural-product scaffolds, revealing mechanistic opportunities that classical screening would likely overlook [32].

4.3. Virtual Screening Approaches

Virtual screening integrates ligand-based and structure-based approaches to evaluate phytochemicals against defined targets. Ligand-based methods use similarity metrics and pharmacophore models to identify compounds with comparable activity profiles, while structure-based methods rely on docking simulations to predict binding affinity and orientation [30]. Docking remains challenging for complex targets such as membrane proteins, including ion channels and GPCRs, due to their dynamic conformational behaviour.

Advances in molecular-dynamics-assisted docking and AI-driven structural prediction have expanded the range of tractable targets and improved the reliability of binding-mode predictions [35,36]. Ligand-based and structure-based screening have been applied to marine-derived metabolites, enabling the identification of novel anti-infective and anticancer candidates with high docking affinity and favourable predicted ADMET profiles [35]. These examples demonstrate how virtual screening opens chemical space that would be inaccessible through extraction alone.

4.4. Hit-to-Lead Optimisation

Hit-to-lead optimisation is traditionally the most resource-intensive phase of preclinical discovery. It requires balancing potency, selectivity, solubility, safety, and pharmacokinetic properties, often with competing objectives. Cheminformatics supports this process by predicting ADMET behaviour, identifying structural liabilities, and guiding rational modification of natural scaffolds [37]. These tools reduce the number of experimental iterations required to achieve an optimal profile and help prioritise compounds with the highest likelihood of success [11]. Digital optimisation frameworks increasingly integrate multi-parameter scoring, enabling simultaneous refinement of potency, safety, and developability.

4.5. Predictive Modelling and Reduction of Late-Stage Attrition

A major challenge in drug discovery is the limited predictive value of traditional in vitro and in vivo models. Many compounds fail during preclinical evaluation due to poor translation from animal models to human biology [38,39]. Computational approaches improve early prediction by integrating structural, biological, and pharmacokinetic data, reducing the risk of late-stage attrition [40]. AI-enhanced models, including deep-learning frameworks and molecular-dynamics simulations, refine predictions of efficacy, toxicity, and target engagement [21]. These approaches support the development of plant-derived compounds with favourable pharmacological profiles and reduce material use [20]. Figure 4 summarises the role of cheminformatics and virtual screening in modern plant-based drug discovery.

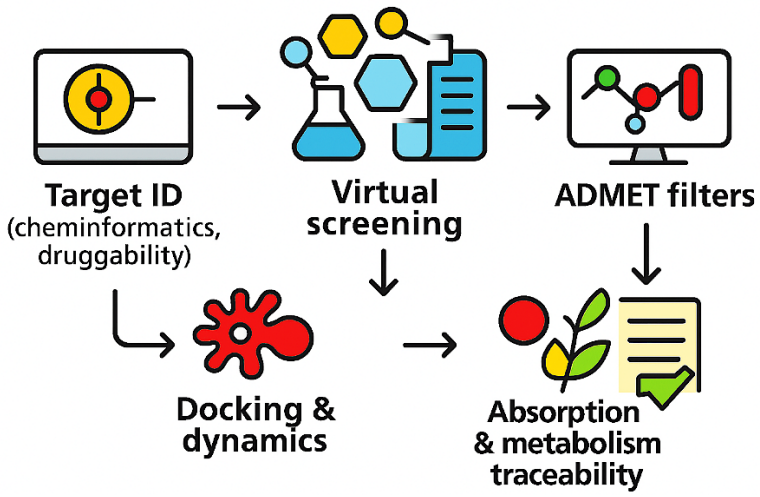

Figure 4. Overview of cheminformatics and virtual screening in modern plant-based drug discovery.

Deep-learning-enhanced docking and molecular-dynamics simulations have recently improved the prediction of binding stability for complex natural-product scaffolds, reducing false-positive rates and supporting more reliable hit-to-lead progression [21,40]. These refinements strengthen confidence in early-stage predictions and reduce the likelihood of costly failures downstream.

5. Artificial Intelligence in Natural Product Drug Discovery

Artificial intelligence has become a central driver of modern drug discovery and now influences every stage of the natural-product development pipeline. Its impact extends from early target identification to translational decision-making, reshaping timelines, prioritisation, and industrial outcomes. Machine-learning models analyse chemical, biological, and pharmacokinetic data at a scale that exceeds traditional computational methods, enabling rapid prediction of compound-target interactions, toxicity, and therapeutic potential [22,41]. These capabilities reduce experimental burden, improve early selection, and create reproducible workflows for natural-product leads [42]. In natural-product research, AI therefore acts both as an accelerator and as an interpreter of complex chemical-biological relationships.

5.1. AI-Enabled Target Prediction

AI-enabled target prediction accelerates one of the most time-consuming phases of discovery. Conventional approaches rely on biochemical assays, genetic studies, and labour-intensive validation, but these methods require extensive resources and often progress slowly. Machine-learning models identify druggable proteins, classify disease-relevant pathways, and predict ligand compatibility using structural and sequence-based features [31,42]. Deep-learning architectures refine these predictions by recognising patterns that are not captured by traditional descriptors, improving accuracy and reducing false-positive rates [21,43]. These tools are particularly valuable for natural-product scaffolds, which often interact with multiple targets and exhibit diverse structural motifs. A landmark demonstration of this capability is the deep-learning-based identification of potent DDR1 kinase inhibitors, where AI models generated natural-product-like scaffolds that were subsequently validated with nanomolar activity [43]. Generative adversarial models have also produced novel anticancer scaffolds with natural-product-like features [44,45]. Related architectures applied to marine polyketides and alkaloids have improved target-class prediction accuracy and pushed early discovery beyond the limits of conventional similarity-based methods [35,41].

5.2. AI-Enhanced Virtual Screening

Virtual screening has been transformed by AI-driven algorithms that evaluate large natural-product libraries with greater speed and precision. Ligand-based models learn from known actives to identify compounds with similar pharmacological profiles, while structure-based models integrate docking scores, molecular-dynamics trajectories, and protein flexibility [30,35]. AI enhances these workflows by predicting binding affinity, ranking candidate molecules, and identifying structural features that influence activity [43]. Generative models extend this capability by designing new analogues inspired by natural scaffolds and optimising potency, selectivity, and physicochemical behaviour simultaneously [11,44,45]. These approaches expand chemical space and support rational modification of natural-product leads. Generative adversarial networks and reinforcement-learning frameworks have produced novel anticancer molecules with natural-product-like architectures, demonstrating how AI can expand chemical diversity while retaining biologically meaningful features [44,45]. In practice, this means that virtual screening no longer simply filters existing libraries but actively proposes new candidates that preserve natural-product-like complexity.

5.3. AI for ADMET and Safety Prediction

ADMET prediction remains a critical component of drug development because limitations in absorption, distribution, metabolism, excretion, and toxicity frequently lead to failure during preclinical or early clinical evaluation. AI models analyse large chemical and biological datasets to predict these parameters with increasing accuracy, allowing early identification of compounds with unfavourable profiles [46]. For natural products, which often possess complex and highly functionalised structures, AI helps identify metabolic hotspots, potential toxicophores, and liabilities that may compromise safety [47,48]. These predictive capabilities reduce reliance on extensive animal testing, guide rational modification of natural scaffolds, and support the selection of candidates with improved pharmacokinetic behaviour. Deep-learning toxicity platforms such as DeepTox and PotentialNet have shown strong performance in predicting hepatotoxicity, cardiotoxicity, and metabolic liabilities for structurally

complex natural products, enabling earlier elimination of unsafe candidates [47,48]. Such models effectively move safety assessment upstream, allowing risk to be managed before substantial experimental investment.

5.4. AI in Translational Decision-Making

AI also influences translational outcomes by integrating chemical, biological, and clinical data to estimate the likelihood of success at each stage of development. Predictive models support portfolio management, prioritise high-value candidates, and reduce the risk of late-stage attrition [49]. Industry-level analyses show that AI shortens preclinical timelines, reduces material use, and improves the efficiency of resource allocation [50]. These benefits are particularly relevant for natural-product research, where structural complexity, multi-target interactions, and limited availability of source material often hinder progress. AI-enabled decision frameworks help determine not only which compounds to pursue, but also when to advance, pause, or discontinue development.

5.5. AI-Driven Multi-Omics Integration

The integration of AI with cheminformatics, network pharmacology, and multi-omics creates a predictive and mechanism-driven framework for natural-product drug discovery. Genomic and transcriptomic datasets reveal biosynthetic capacity, proteomic profiles identify pathway activity, and metabolomic fingerprints link chemical diversity to environmental and genetic factors [51]. AI models synthesise these heterogeneous datasets to identify new biosynthetic pathways, predict metabolite production, and guide metabolic engineering [25,52]. These capabilities support sustainable sourcing, improve yields of rare compounds, and expand the chemical diversity available for discovery [6]. Figure 5 illustrates the role of artificial intelligence in plant-based drug discovery.

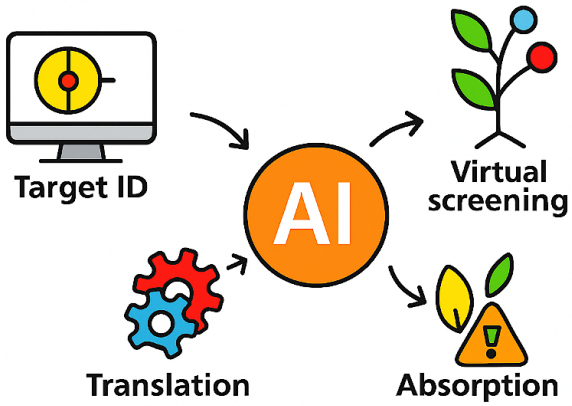

Figure 5. Role of artificial intelligence in plant-based drug discovery.

AI-enabled integration of metabolomic and transcriptomic datasets has accelerated pathway discovery in medicinal plants. Machine-learning models have linked gene-cluster expression to metabolite accumulation, enabling targeted metabolic engineering and improving yields of bioactive compounds [20,26,51]. Comparable approaches have been applied to diterpenoid pathways in Taxus species, identifying rate-limiting enzymatic steps relevant to paclitaxel biosynthesis [6,27]. Automated Design-Build-Test-Learn pipelines further support microbial production of plant-derived metabolites [52]. Collectively, these strategies demonstrate how AI can convert complex multi-omics data into actionable designs for both plant and microbial production systems.

6. Case Studies: Industrial Success Stories

The industrial success of natural-product-derived pharmaceuticals demonstrates the translational value of computational methodologies in modern drug discovery. Foundational analyses confirm that natural products continue to supply clinically important scaffolds, while digital tools accelerate their optimisation, mechanistic interpretation, and development [6,16]. Informatics-driven workflows, including cheminformatics, artificial intelligence, network pharmacology, and multi-omics, support the identification, refinement, and repurposing of natural-product leads across therapeutic areas [35,53]. These case studies show how traditional knowledge, analytical science, and computational platforms intersect to deliver clinically validated and commercially successful therapeutics, as illustrated by artemisinin, paclitaxel, aspirin, morphine, and digoxin [54–56]. Figure 6 outlines how landmark natural-product drugs progressed from traditional sources to clinically validated therapeutics through computational and experimental refinement.

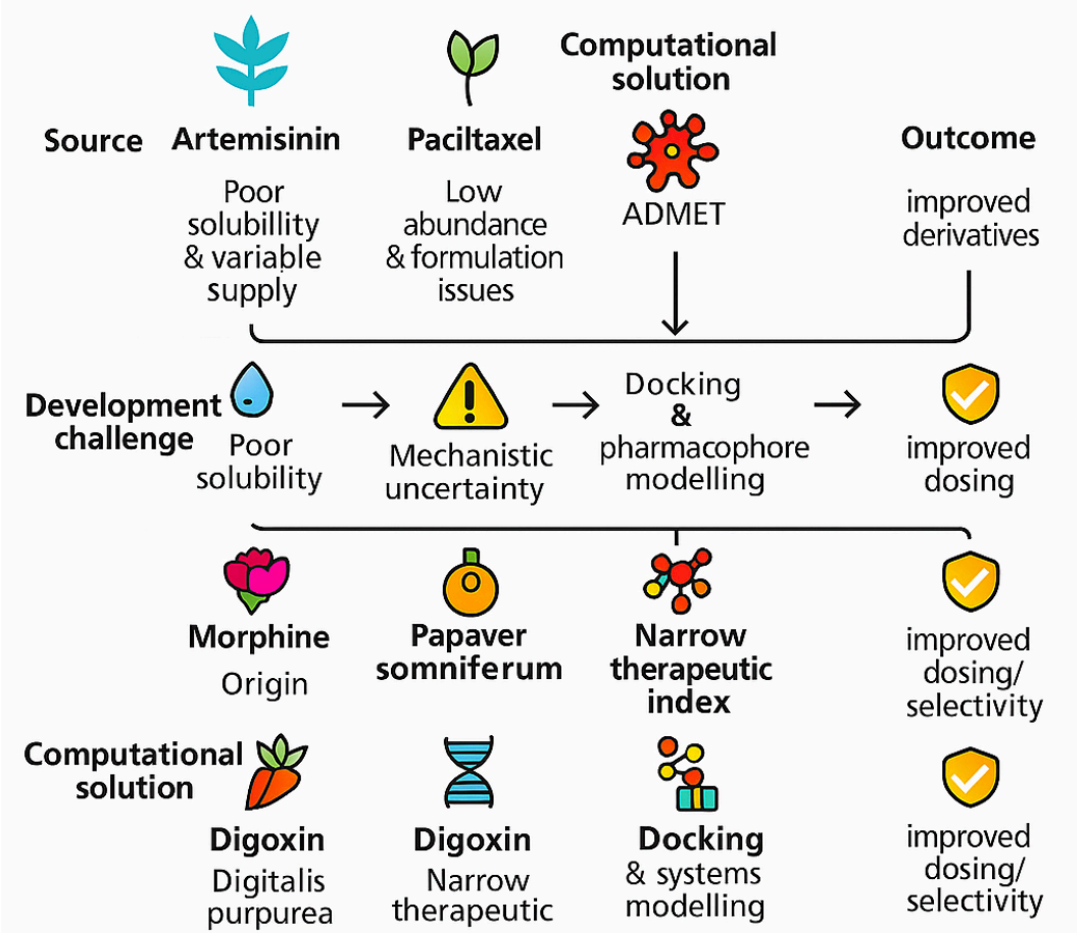

Figure 6. Translational pathways of landmark natural-product drugs.

6.1. Artemisinin

Artemisinin, a sesquiterpene lactone from *Artemisia annua*, transformed global malaria treatment and remains the most effective agent against *Plasmodium falciparum* [54]. Development was hindered by solubility limitations and supply constraints. Computational docking and network-based analyses clarified haem-mediated cleavage and reactive-oxygen-species pathways, supporting the rational design of derivatives with improved potency, stability, and bioavailability [35,57]. Systems-level multi-omics studies identified regulatory nodes in the MEP pathway, enabling targeted metabolic-engineering strategies that increased artemisinin yield and reduced agricultural dependency [58,59]. These digital insights complemented traditional pharmacology and helped accelerate the transition from empirical extraction to artemisinin-based combination therapies (ACTs), adopted by WHO in 2001.

6.2. Paclitaxel

Paclitaxel, a diterpenoid from *Taxus brevifolia*, is a cornerstone therapy for ovarian, breast, and lung cancers [55,56]. Its development was challenged by low natural abundance, structural complexity, and formulation difficulties. Docking and ADMET modelling guided analogue design and improved therapeutic indices, while *in silico* screening identified synergistic combinations and new targets that strengthened its role in multidrug regimens [35,60,61]. Network pharmacology clarified interactions with microtubule stabilisation, cell-cycle arrest, and apoptosis pathways, supporting rational optimisation of dosing strategies [57]. Multi-omics and genome-editing approaches identified rate-limiting steps in diterpenoid biosynthesis, enabling CRISPR-based optimisation and improving industrial yields [27,62]. These computational contributions refined development but did not replace the clinical pathway that culminated in FDA approval in 1992.

6.3. Aspirin

Aspirin, historically derived from *Salix alba*, represents one of the earliest natural product scaffolds adapted for synthetic drug development. Salicin was chemically transformed into acetylsalicylic acid in the late nineteenth

century. Although its discovery predates computational science, modern docking and pharmacophore analyses have clarified COX-1 and COX-2 binding mechanisms, informing the development of COX-selective inhibitors and antiplatelet agents [16,60,63]. This case illustrates how legacy natural-product drugs continue to benefit from contemporary digital tools, even when their origins lie far outside the computational era.

6.4. Morphine

Morphine, an isoquinoline alkaloid from *Papaver somniferum*, remains a reference standard for severe pain management. Molecular-dynamics simulations and receptor-binding models have clarified its interactions with μ-opioid receptor subtypes, guiding the design of safer, biased, and subtype-selective agonists [35,53]. Pharmacokinetic modelling and ADMET tools supported the development of extended-release formulations and improved safety profiles [60]. Synthetic-biology and multi-omics strategies now aim to reconstruct morphine biosynthesis in microbial hosts, reducing reliance on traditional cultivation and strengthening supply-chain resilience [6]. These computational advances refine both mechanistic understanding and production strategies, while the drug's nineteenth-century clinical introduction remains unchanged.

6.5. *Digoxin*

Digoxin, a cardiac glycoside from *Digitalis purpurea*, remains central to cardiovascular therapy. Its mechanism involves inhibition of Na^+/K^+-ATPase, leading to increased intracellular calcium and enhanced cardiac contractility. Computational docking and molecular-dynamics simulations have elucidated its binding interactions, guiding the design of analogues with improved selectivity and reduced toxicity. Network pharmacology has revealed additional targets in cardiac-signalling pathways, supporting its use in heart failure and atrial fibrillation [7,11,64]. Metabolic-engineering efforts have optimised glycoside production in plant cell cultures, addressing supply limitations from traditional sources [20,27]. These contributions enhance mechanistic clarity and production efficiency but complement, rather than replace, the historical clinical development of digoxin. Table 1 highlights the computational contributions to landmark natural product drugs.

Table 1. Computational contributions to landmark natural product drugs.

Natural Product (Source Plant; Uses)	Key Development Challenge	Key Computational Contribution	Reference
Artemisinin (*Artemisia annua*; antimalarial)	Poor solubility; variable supply	Docking clarified activation; multi-omics identified pathway bottlenecks; models guided derivative optimisation.	[35,54,57–59]
Paclitaxel (*Taxus brevifolia*; anticancer)	Low abundance; structural complexity	Docking/ADMET supported analogue design; network pharmacology mapped mechanisms; multi-omics enabled CRISPR-based yield improvement.	[27,35,55,56,60–62]
Aspirin (*Salix alba*; analgesic, anti-inflammatory, antiplatelet)	Mechanism initially unclear	Docking and pharmacophore modelling refined COX-1/COX-2 interactions.	[16,60,63]
Morphine (*Papaver somniferum*; analgesic)	Safety and dependence risk	Molecular-dynamics clarified receptor binding; ADMET informed safer formulations; multi-omics supported biosynthetic reconstruction.	[6,35,53,60]
Digoxin (*Digitalis purpurea*; cardiovascular)	Narrow therapeutic index	Docking/MDS clarified Na^+/K^+-ATPase binding; network pharmacology identified secondary cardiac targets; metabolic engineering improved production.	[7,11,20,27,35]

7. Bioactivity Screening and Mechanism of Action

Bioactivity screening provides the first experimental evidence of natural-product activity and guides the transition from computational prediction to laboratory validation. Modern workflows integrate virtual screening, ADMET prediction, target identification, and mechanistic modelling to prioritise high-value candidates and clarify their biological relevance. These approaches reduce experimental burden, improve early decision-making, and support the development of natural product leads with defined mechanistic profiles. Recent work across kinase inhibitors, alkaloids, and botanical extracts shows how AI-guided prioritisation and network-based analysis now shape early discovery decisions [21,35,41].

7.1. Network Pharmacology and Multi-Target Mechanisms

Network pharmacology represents a paradigm shift in understanding natural-product pharmacology, which often involves multi-target effects rather than single-target specificity. This approach models compound-target-pathway-disease relationships as interconnected networks, revealing synergistic interactions and clarifying how

complex mixtures achieve therapeutic outcomes [6,7]. Tools such as Cytoscape and STRING integrate data from KEGG and STRING to visualise these interactions [65]. Applications in traditional Chinese medicine have demonstrated how multi-component formulations modulate several pathways in diseases such as cancer and diabetes. AI-enabled network construction has strengthened target-ranking accuracy and uncovered pathway nodes that were previously overlooked in natural-product datasets [36]. The experimental validation remains essential for confirming network-derived hypotheses [36,65]. Figure 7 outlines the computational screening funnel that prioritises natural-product candidates and clarifies their mechanistic relevance.

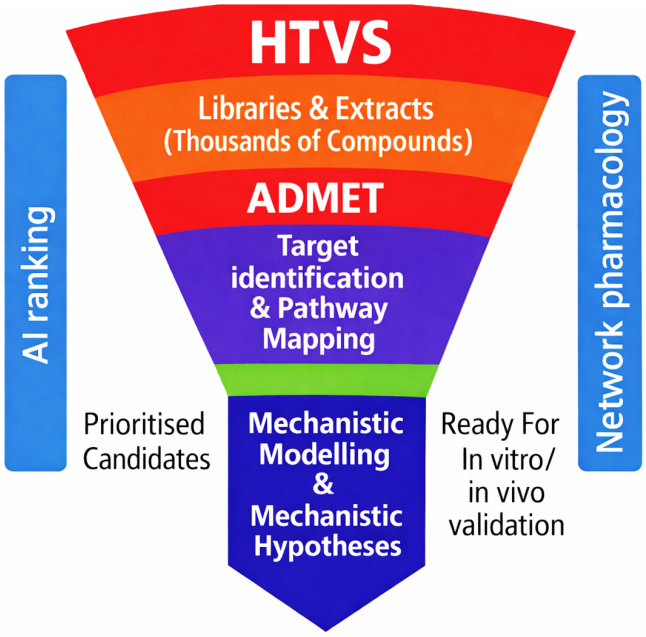

Figure 7. Computational screening funnel for natural-product bioactivity and mechanism of action.

7.2. High Throughput Virtual Screening (HTVS)

High-throughput virtual screening evaluates large natural-product libraries against defined biological targets using docking, pharmacophore modelling, and ligand-based similarity methods. Platforms such as AutoDock Vina, MOE, and Glide simulate thousands of compounds-target interactions within short timeframes, enabling early identification of promising scaffolds [12,57]. These approaches help deconvolute complex mixtures, prioritise active constituents, and exclude weak binders before laboratory testing. HTVS campaigns have highlighted diterpenoid and alkaloid candidates with predicted nanomolar affinity, demonstrating the value of combining docking with machine-learning-based scoring functions [35,43].

7.3. ADMET and Pharmacokinetic Profiling

ADMET profiling remains essential for assessing the drug-likeness of natural-product candidates. *In silico* platforms such as SwissADME, pkCSM, and ADMETlab integrate structural and physicochemical descriptors with machine-learning models to predict solubility, permeability, metabolic stability, and toxicity [60,61]. Early ADMET filtering enriches for compounds with favourable bioavailability and safety, reducing the risk of late-stage attrition. Deep-learning toxicity frameworks have improved prediction of hepatotoxicity and cardiotoxicity for structurally complex natural products, enabling safer and more selective lead prioritisation [47,48].

7.4. Target Identification and Pathway Mapping

Target identification is central to understanding the molecular basis of natural-product activity. Reverse docking, machine-learning-based prediction, and proteome-wide screening approaches map small molecules to potential protein targets [35,63]. Pathway-enrichment analysis using KEGG, Reactome, and Gene Ontology clarifies the biological processes affected by the compound [35,58], revealing multi-target interactions and supporting repurposing strategies. Hybrid pipelines that combine reverse docking with network pharmacology have identified secondary targets for cardiac glycosides and diterpenoids, strengthening mechanistic interpretation and translational relevance [11,27].

7.5. Mechanistic Modelling and Systems Pharmacology

Mechanistic modelling integrates structural, biochemical, and pharmacokinetic data to simulate the effects of natural products on cellular networks. Systems pharmacology combines network pharmacology, pharmacodynamics, and multi-omics data to characterise drug action at multiple biological scales [11,26,58]. These models capture receptor-ligand dynamics, enzyme kinetics, feedback loops, and pathway cross-talk, supporting hypothesis generation and rational analogue design. System-level simulations have clarified microtubule-stabilising mechanisms of paclitaxel analogues and predicted off-target effects of alkaloids, demonstrating how computational modelling strengthens mechanistic confidence before in vivo testing [57,62].

8. Multi-Omics and Systems Biology in Natural Product Drug Discovery

Multi-omics and systems biology now underpin modern natural-product drug discovery by linking chemical diversity to genetic, metabolic, and regulatory networks. These approaches provide a comprehensive view of how natural products are produced, how they vary across environments, and how they influence biological systems at multiple organisational levels. Genomic, transcriptomic, proteomic, and metabolomic datasets clarify biosynthetic capacity, chemical composition, and regulatory dynamics, while system-level models integrate these layers to explain how natural products modulate complex biological pathways. Recent work on diterpenoid pathways in *Taxus* species and tanshinone biosynthesis in *Salvia miltiorrhiza* illustrates how multi-omics reshapes both mechanistic understanding and production strategies [20,26,27]. Figure 8 illustrates an integrated network map showing how a natural-product scaffold connects to predicted protein targets, pathway-level mechanisms, and disease-network convergence. Coloured node clusters represent four mechanistic domains: synergy, repurposing, pathway convergence, and pathways and disease networks.

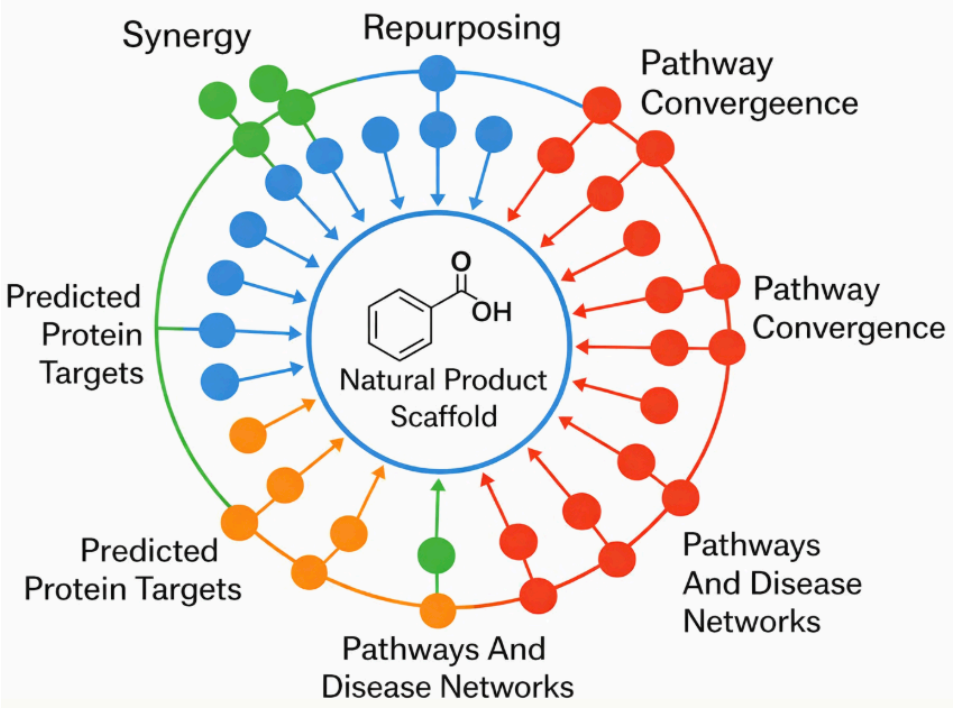

Figure 8. Systems-level network architecture of natural-product interactions.

8.1. Genomics, Transcriptomics, and Biosynthetic Capacity

Genomics provides the foundation for understanding natural-product biosynthesis by identifying gene clusters responsible for secondary-metabolite production [21,22]. These clusters encode enzymes that assemble, modify, and diversify natural-product scaffolds, and their organisation often reflects evolutionary adaptation to ecological pressures. Comparative genomics reveals species-specific variations in pathway architecture, supporting authentication and guiding the selection of high-yielding or chemically rich taxa. Transcriptomics complements this by capturing gene-expression patterns that regulate biosynthetic pathways under different physiological or environmental conditions. Stress, developmental stage, and ecological interactions influence pathway activation, and transcriptomic data reveal how these factors shape metabolite profiles. Together, these datasets expose regulatory bottlenecks, highlight inducible pathways, and guide metabolic-engineering strategies

aimed at enhancing the production of valuable metabolites. Examples include transcriptome-guided identification of rate-limiting enzymes in paclitaxel biosynthesis and stress-responsive activation of phenylpropanoid pathways in medicinal plants [20,27,62].

8.2. Proteomics, Metabolomics, and Chemical Diversity

Proteomics characterises the enzymatic machinery that drives natural-product formation. Enzyme abundance, post-translational modification, and protein-protein interactions influence pathway efficiency and determine which metabolites accumulate in biological material [14,15]. These datasets identify rate-limiting steps and regulatory nodes that can be targeted to improve biosynthetic output. Metabolomics provides a direct chemical fingerprint of the organism, capturing both abundant and low-abundance constituents. These profiles support authentication, quality control, and the identification of bioactive metabolites. Metabolomic comparisons across tissues, developmental stages, or environmental conditions reveal how chemical diversity emerges from dynamic biosynthetic regulation. When proteomic and metabolomic layers are examined together, enzymatic activity can be directly linked to chemical outcomes, clarifying pathway flux and metabolite diversification. Recent studies have used this combined perspective to explain diterpenoid diversification in Taxus species and to identify minor bioactive metabolites in complex botanical extracts [20,27].

8.3. Systems Biology and Mechanistic Integration

Systems biology unifies multi-omics datasets to model how natural products influence cellular networks. This perspective moves beyond reductionist paradigms and captures the dynamic interplay between pathways, feedback loops, and regulatory nodes. For complex diseases, where multiple pathways contribute to pathology, system-level models reveal how natural products modulate interconnected processes and identify points of convergence that explain therapeutic outcomes [11,58]. These models incorporate receptor-ligand dynamics, enzyme kinetics, transcriptional regulation, and metabolic flux, providing a mechanistic framework that connects chemical structure to biological function. Network-based analyses further refine these insights by mapping compound-target-pathway relationships and clarifying how multi-component mixtures exert coordinated effects. Systems-level modelling, therefore, supports hypothesis generation, analogue design, and the rational development of multi-target interventions. Recent applications include predictions of microtubule-stabilising effects of paclitaxel analogues and mapping of anti-inflammatory signalling networks modulated by diterpenoids [57,62].

8.4. AI-Enabled Multi-Omics Interpretation and Future Directions

Artificial intelligence accelerates the interpretation of large multi-omics datasets by identifying patterns that are not readily apparent through conventional analysis. Machine-learning models predict biosynthetic capacity, identify uncharacterised gene clusters, and infer regulatory relationships that influence metabolite production [25,51,52]. Deep-learning architectures integrate genomic, proteomic, and metabolomic data to predict pathway activity and uncover previously unrecognised biosynthetic routes that expand the chemical space available for discovery. AI-guided interpretation of multi-omics data now supports sustainable innovation by directing metabolic engineering, improving yields of rare metabolites, and reducing reliance on endangered species. These approaches also strengthen mechanistic interpretation by linking chemical diversity to biological outcomes with increasing accuracy. Recent AI-driven DBTL (Design-Build-Test-Learn) pipelines have accelerated microbial production of plant-derived metabolites and improved optimisation cycles for complex biosynthetic pathways [52]. As computational tools continue to advance, multi-omics-driven discovery will become more predictive, more sustainable, and more deeply integrated with industrial development.

9. Industrial Applications and Commercialisation of Natural Product-Derived Products

Industrial-scale development of natural-product-derived products depends on coordinated strategies for sourcing, extraction, formulation, and regulatory compliance. Sourcing must ensure consistent quality and supply, often through controlled cultivation, contract farming, or biotechnological production systems that reduce variability and strengthen traceability [3,27]. Extraction methods such as solvent extraction and supercritical fluid extraction isolate bioactive constituents with defined purity, while formulation establishes dosage forms that maintain stability, bioavailability, and therapeutic performance [3,27]. These steps form a structured pathway that links laboratory discovery to commercial deployment. Across this pathway, computational tools increasingly support quality prediction, metabolite profiling, and process optimisation, creating more reproducible and time-

efficient industrial pipelines [35,52]. Figure 9 depicts the bench-to-market trajectory that connects sourcing, extraction, formulation, regulation, and industrial production of natural-product-derived products.

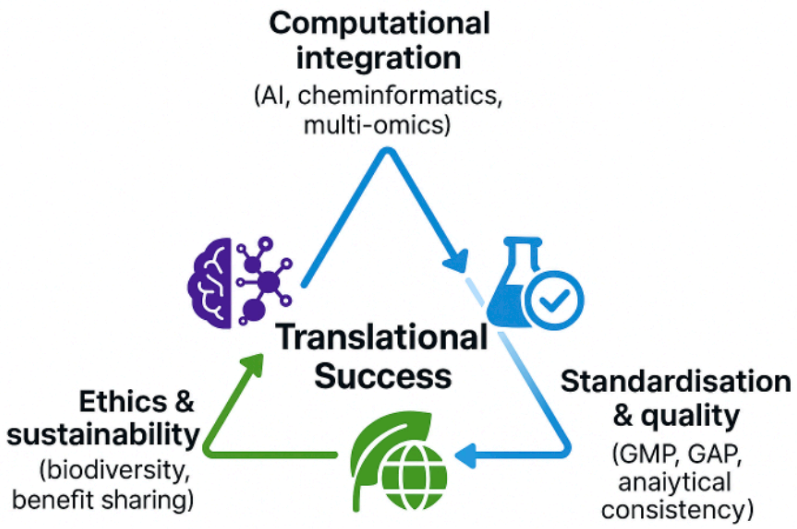

Figure 9. Industrial development pathway for natural-product-derived products.

9.1. Regulatory and Quality Control Considerations

Manufacturing of natural-product-derived products operates within regulatory frameworks designed to safeguard safety, efficacy, and quality [3,64]. Agencies such as the FDA and EMA outline requirements for registration, standardised extraction, analytical validation, and clinical evidence. Quality-control procedures, including chemical profiling, stability testing, and batch-to-batch comparison, ensure reproducibility and maintain compliance with international standards. Computational platforms now assist these processes by predicting chemical stability, flagging adulteration risks, and guiding analytical-method development [35,60]. These regulatory expectations support consumer confidence and facilitate global market access.

9.2. Intellectual Property and Market Trends

Commercialisation requires careful management of intellectual property, including patents, trademarks, and trade secrets [66,67]. Patents protect novel formulations, extraction processes, and delivery systems, while trademarks strengthen brand identity and market differentiation. The global market for natural-product-derived products continues to expand, driven by increasing consumer interest in natural health solutions and plant-based alternatives [68,69]. Current trends show strong demand for nutraceuticals, functional foods, and cosmeceuticals, reflecting a broader shift toward preventive health and wellness. AI-enabled market analytics now support trend forecasting, consumer-behaviour modelling, and competitive-landscape assessment, informing strategic product positioning [68].

9.3. Pharmaceutical Industry Applications

The pharmaceutical industry continues to rely on natural-product scaffolds, with several landmark drugs originating from natural sources [55,69]. Artemisinin, paclitaxel, and aspirin remain notable examples that have reshaped modern medicine [54,56,70]. Computational tools and multi-omics technologies now strengthen natural-product drug development by identifying new compounds, predicting targets, clarifying mechanisms, and guiding analogue optimisation [3,27]. These advances reduce development timelines and support the discovery of next-generation therapeutics. In practice, these digital tools refine and accelerate development but complement, rather than replace, the historical discovery pathways that brought these drugs to market. Recent industrial pipelines increasingly integrate AI-enabled virtual screening, ADMET prediction, and biosynthetic-engineering models to shorten preclinical timelines and improve success rates [21,35,43].

9.4. Nutraceuticals, Functional Foods, and Cosmeceuticals

Nutraceuticals attract significant interest because many natural-product constituents demonstrate antioxidant, anti-inflammatory, or immune-modulating activity in preclinical and clinical studies [68,69]. Functional foods

incorporate defined bioactive compounds to enhance nutritional value and support specific physiological functions. Cosmeceuticals apply similar principles to skin and hair care, combining cosmetic formulation with biologically active natural-product ingredients. Development across these categories follows structured formulation, analytical validation, and clinical assessment to ensure consistent performance, safety, and regulatory compliance [68,69]. Computational metabolomics and chemometric profiling now support ingredient authentication, adulteration detection, and formulation optimisation, strengthening product reliability and market competitiveness [35].

9.5. Agricultural and Environmental Applications

Sustainable sourcing of natural-product-producing species remains essential for long-term availability [64,67]. Conservation strategies, including controlled cultivation, regulated wild harvesting, and habitat protection, safeguard vulnerable species and maintain ecological balance. Agricultural biotechnology, including CRISPR-Cas9 and other genome-editing tools, strengthens the production of bioactive compounds and reduces reliance on natural populations [62]. Multi-omics-guided breeding and AI-enabled trait-prediction models now support the selection of high-yielding chemotypes and stress-resilient cultivars, improving agricultural sustainability [20,27]. These approaches support sustainable development, secure future supply, and align with global environmental priorities.

10. Emerging Technologies and Innovations in Natural Product Development

Emerging technologies continue to reshape natural-product research by improving precision, efficiency, and sustainability across discovery, optimisation, and formulation. The integration of genomics, proteomics, and metabolomics has clarified biosynthetic pathways and strengthened understanding of their therapeutic relevance. Genomic datasets identify genes responsible for secondary-metabolite production, while proteomic and metabolomic profiles reveal changes in protein expression and metabolic activity under different physiological or environmental conditions [11,26,58]. These platforms support the discovery of new metabolic routes, guide metabolic engineering, and enhance the production of bioactive compounds. Recent advances, ranging from CRISPR-Cas9 to nanotechnology, artificial intelligence, and 3D printing, extend these capabilities by enabling targeted pathway modification, improved delivery, predictive modelling, and personalised formulation. Figure 10 highlights the four technological pillars that shape next-generation natural-product discovery and development.

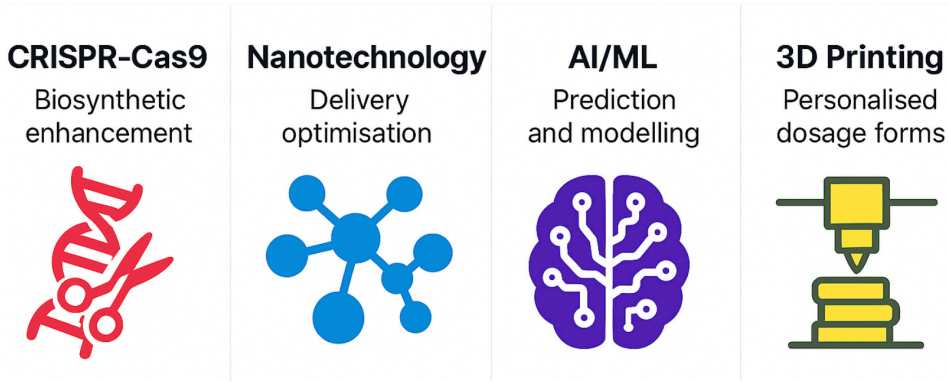

Figure 10. Emerging technological pillars in natural-product innovation.

10.1. CRISPR-Cas9 and Genetic Engineering

CRISPR-Cas9 has become a precise tool for modifying genes involved in the biosynthesis of medicinally important natural products. Targeted editing of biosynthetic genes increases the production of compounds such as artemisinin and paclitaxel in engineered biological systems [62]. This approach reduces dependence on traditional extraction methods, which often require extensive resources and place pressure on natural populations. CRISPR-enabled metabolic engineering therefore supports scalable, cost-effective, and sustainable production of high-value natural-product compounds [62]. CRISPR-enabled pathway optimisation therefore supports scalable, cost-effective, and sustainable production of high-value natural-product compounds.

10.2. Nanotechnology in Drug Delivery

Nanotechnology strengthens natural-product delivery by improving solubility, stability, and targeted distribution of structurally complex compounds [60]. Nanocarriers such as liposomes, polymeric nanoparticles,

and dendrimers encapsulate natural-product scaffolds, protect them from degradation, and enhance absorption. Targeted delivery reduces off-target effects and improves therapeutic outcomes. These platforms address long-standing challenges associated with poor bioavailability and rapid metabolism, reinforcing the clinical potential of natural-product-based therapeutics.

10.3. Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning now contribute to predictive modelling, virtual screening, and formulation optimisation [35,36]. Deep-learning models and generative frameworks analyse large datasets to predict bioactivity, toxicity, and pharmacokinetic behaviour. These tools accelerate candidate identification and shorten development timelines. When combined with multi-omics datasets, AI improves pathway prediction, supports biosynthetic-engineering strategies, and enables the design of targeted and personalised natural-product therapies [36].

10.4. 3D Printing and Personalised Medicine

3D printing supports the development of personalised dosage forms tailored to individual patient needs. This technology provides precise control over drug-release profiles, enabling sustained-release, immediate-release, or targeted-delivery formats [71]. Dosage forms can be adjusted according to patient-specific factors such as age, weight, and comorbidities. The incorporation of 3D printing into natural-product development strengthens patient-centred care and expands opportunities for customised therapeutic interventions [71]. Incorporating 3D printing into natural-product development strengthens patient-centred care and expands opportunities for customised therapeutic interventions.

11. Future Directions in Natural Product Development

The future of natural-product drug discovery rests on deeper integration of computational and experimental approaches. Cheminformatics, artificial intelligence, and network pharmacology accelerate early identification and prediction of bioactive compounds, while experimental validation ensures accuracy and translational relevance [16,36]. Multi-omics platforms refine this process by linking genomic, proteomic, and metabolomic data to biosynthetic pathways and therapeutic potential [11,26,58]. These combined approaches shorten development timelines, improve predictive confidence, and support the progression of promising candidates toward market-ready products [16,36]. Emerging frameworks now place equal emphasis on sustainability, standardisation, and computational optimisation, ensuring that natural-product development remains both scientifically rigorous and industrially viable. Figure 11 depicts the future-oriented framework that integrates computational innovation, standardisation, and sustainability to support translational success. Figure 11 depicts the future-oriented framework that integrates computational innovation, standardisation, and sustainability to support translational success.

Figure 11. Future-focused framework for natural-product drug development.

11.1. Standardisation and Quality Control

Standardisation and quality control remain central to the safety, efficacy, and reproducibility of natural-product-derived products [3,64]. Consistent sourcing, extraction, and formulation protocols minimise variability in chemical composition and support reliable therapeutic performance [3,27]. Quality-control procedures such as chemical profiling, stability testing, and batch-to-batch comparison strengthen product consistency and ensure compliance with regulatory expectations [3,64]. Good Manufacturing Practices and Good Agricultural Practices reinforce consumer confidence and align natural-product development with international standards, while computational chemometrics and AI-based quality-prediction models increasingly support real-time monitoring and early detection of variability.

11.2. Ethical and Sustainability Considerations

Ethical and sustainable development protects biodiversity and respects traditional knowledge. Overharvesting and inequitable use of indigenous knowledge raise significant ethical concerns [68,69]. Sustainable sourcing strategies, including regulated wild harvesting, expanded cultivation, and habitat protection, support long-term availability of natural-product-producing species [64,67]. Equitable benefit-sharing agreements ensure that communities contributing traditional knowledge receive appropriate recognition and compensation, strengthening the ethical foundations of natural-product development. Equitable benefit-sharing agreements ensure that communities contributing traditional knowledge receive appropriate recognition and compensation, strengthening the ethical foundations of natural-product development. Sustainability-focused computational tools, including ecological modelling and species-distribution prediction, increasingly guide conservation-aligned sourcing decisions.

11.3. Bridging the Evidence Gap

A persistent challenge in natural-product drug discovery is the gap between preclinical promise and clinical validation [3,27]. Many natural-product compounds demonstrate strong preclinical activity but lack rigorous clinical evidence. Integrating computational prediction, multi-omics analysis, and experimental validation strengthens translational pathways and improves the likelihood of clinical success [16,36]. Translational research frameworks support efficient progression from laboratory findings to clinical evaluation, ensuring that high-value candidates advance through regulatory pathways with greater speed and confidence [3,27]. Computational phytochemistry has emerged as a transformative extension of traditional natural-product research, enabling rapid dereplication, structural prediction, and activity modelling through integrated cheminformatics and machine-learning tools [24]. These innovations help prioritise clinically relevant candidates, reduce redundancy, and clarify mechanistic plausibility before costly clinical testing.

12. Limitations of Computational Approaches in Natural Product Drug Discovery

Computational approaches have transformed natural product drug discovery, yet they remain constrained by several methodological and translational limitations that affect predictive accuracy and industrial applicability. Data quality and bias remain major challenges, as natural product databases often contain incomplete, inconsistent, or poorly annotated structures, limiting the reliability of cheminformatics filters and machine-learning models [72,73]. Structural diversity in natural products also exceeds that of synthetic libraries, and current descriptors may not fully capture stereochemistry, conformational flexibility, or unusual scaffolds [74].

False positives and over-prediction are common across docking, virtual screening, and AI-based models, particularly when applied to flexible proteins, membrane-embedded targets, or multi-component mixtures [75,76]. Docking scores frequently fail to correlate with biological activity, and AI models trained on biased datasets may overfit or misclassify natural product scaffolds, reducing generalisability [73,75].

Multi-component systems remain difficult to model, even with advanced network-pharmacology and system-biology frameworks. These tools can map interactions, but they cannot yet fully capture emergent properties such as synergy, antagonism, or context-dependent effects, which are central to botanical extracts and traditional formulations [76,77]. This limitation is particularly relevant for complex mixtures used in ethnopharmacology and TCM, where multi-target effects are essential to therapeutic action [77].

Clinical translation remains limited, despite improvements in early prediction. Few natural product leads progress to clinical trials because computational models cannot yet account for complex pharmacokinetics, inter-individual variability, or long-term safety, all of which require extensive experimental and clinical validation [73,77]. Predictive tools accelerate prioritisation but cannot replace the need for robust in vivo and clinical evidence [73].

Regulatory and standardisation challenges persist, especially for multi-component natural product preparations. Computational predictions alone cannot satisfy regulatory requirements for safety, efficacy, and reproducibility, and agencies continue to demand rigorous analytical validation and clinical data [73,74]. These constraints slow the translation of computationally prioritised candidates into approved therapeutics.

Sustainability and supply-chain constraints continue to influence development, even when computational tools identify promising scaffolds. Limited availability of source species, ecological vulnerability, and geopolitical factors may restrict scalability, requiring integration of synthetic biology, metabolic engineering, and sustainable sourcing strategies [74,77]. Overall, computational approaches enhance, but cannot replace, experimental validation, regulatory oversight, and sustainable sourcing. Their value lies in accelerating prioritisation, guiding mechanistic interpretation, and supporting rational design within an integrated discovery pipeline [72,76].

Future natural-product development demands a multidimensional framework that integrates technological acceleration, ethical responsibility, and ecological sustainability. Figure 12 illustrates six interlinked priorities that collectively shape this evolving landscape, such as computational acceleration, multi-omics integration, standardisation and quality control, ethics and sustainability, evidence-gap bridging, and sustainable sourcing with biodiversity preservation. These domains converge to support a more predictive, validated, and ethically grounded pipeline for natural-product innovation.

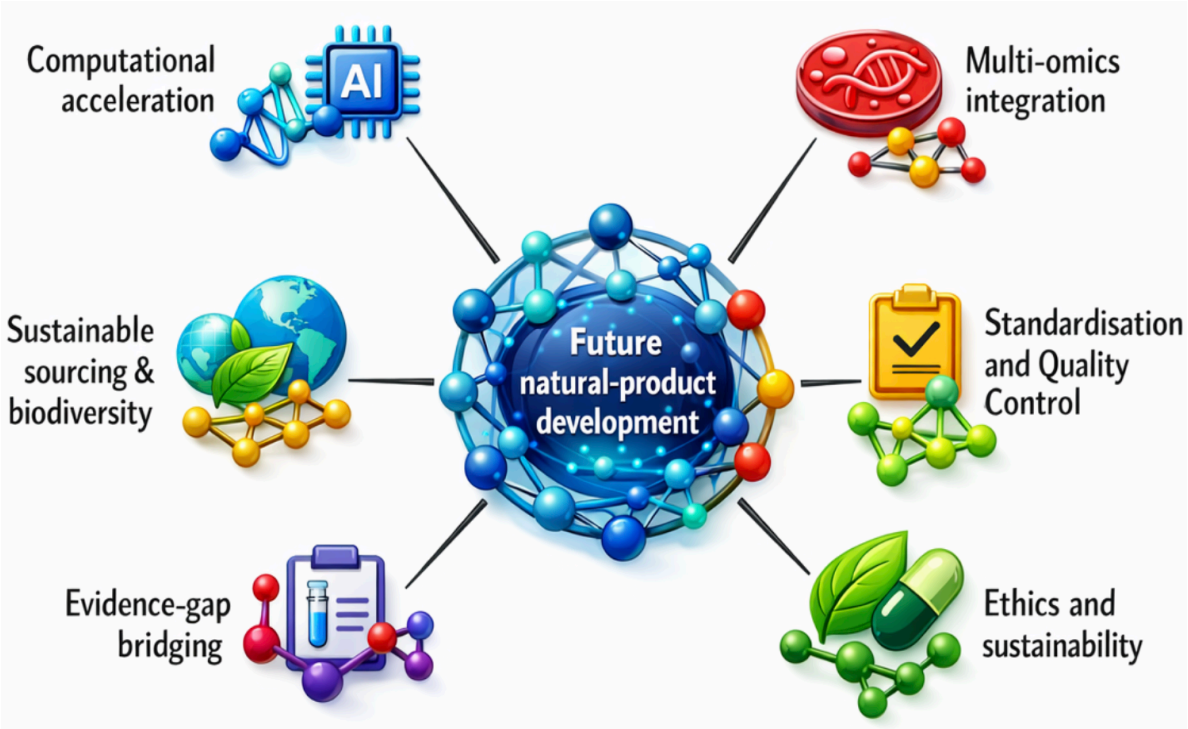

Figure 12. Multidimensional priorities for future natural-product development.

13. Conclusions

This review explores how computational tools have reshaped natural-product drug discovery by introducing precision, efficiency, and sustainability into every stage of development. Cheminformatics, artificial intelligence, network pharmacology, and multi-omics integration accelerate the identification and prediction of bioactive compounds, reducing reliance on trial-and-error experimentation. These technologies support the discovery of new therapeutic candidates, strengthen mechanistic interpretation, and guide the development of reproducible, high-value natural-product-based medicines. As emerging innovations such as CRISPR-Cas9, nanotechnology, and advanced modelling continue to mature, they will further expand the possibilities for targeted optimisation and personalised formulation. Sustained progress will depend on rigorous regulatory standards, ethical sourcing, and a commitment to sustainability, ensuring that natural-product-derived therapeutics are developed responsibly and deliver meaningful global benefit.

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