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FROM EMPIRICAL HERBAL MEDICINE TO PREDICTIVE THERAPEUTICS: THE ROLE OF AI AND MULTI-OMICS

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ABSTRACT

Purpose: Medicinal plants are the richest source of structurally diverse biologically active compounds. Herbal leads discovery can also be accelerated using artificial intelligence and multi omics technologies. This review evaluates and summarizes the applications of artificial intelligence (AI), multi-omics, synthetic biology, and biomanufacturing in advancing research for herbal therapeutics. Virtual computational screening, deep learning, and molecular docking extremely accelerate lead identifications, structure-activity predictions, and target identification. **Method:** We comprehensively examine literature on virtual computational screening, deep learning, molecular docking, multi-omics platforms, genome mining, CRISPR-based synthetic biology, and emerging tools like organ-on-a-chip systems and nanobiotechnology using PubMed, ScienceDirect and Google Scholar. **Result:** Virtual screening, deep learning, and molecular docking extremely accelerate lead identifications, structure-activity predictions, and target identification. Simultaneously, multi-omics platforms evaluate system-level metabolic networks, regulatory pathways, and host–microbiome interactions. Genome mining and CRISPR-based synthetic biology unlock cryptic metabolic pathways and enable scalable, sustainable production of

high-value natural products. Furthermore, tools like organ-on-a-chip systems and nanobiotechnology bridge the gap toward precision herbal medicine and standardization. **Conclusion:** By integrating these multidisciplinary strategies, herbal drug discovery is evolving from empirical observation toward predictive, sustainable, and mechanism-driven pharmaceutical science. Finally, key challenges like data standardization, explainable AI, experimental validation, and regulatory approval must be addressed for clinical translation.

KEYWORDS: Artificial intelligence; Natural products; Drug discovery; Multi-omics; Synthetic biology; Genome mining; Biotechnology; Metabolic engineering

1. INTRODUCTION

Natural products have been an important source of therapeutic agents for centuries and continue to play a crucial role in modern drug discovery. The extraordinary biodiversity of terrestrial and marine ecosystems continues to provide an immense reservoir of structurally unique natural products that remain largely unexplored for pharmaceutical applications.[1] Compounds derived from plants, microorganisms, marine organisms, and animals possess remarkable chemical diversity and biological activity, making them valuable sources of novel drug candidates.[2] Several clinically important drugs, including morphine, quinine, paclitaxel, artemisinin, penicillin, and cyclosporine, originated directly or indirectly from natural sources, highlighting the significant contribution of natural products to pharmaceutical development.[3] Their unique molecular structures and diverse pharmacological properties continue to provide promising scaffolds for the treatment of cancer, infectious diseases, cardiovascular disorders, metabolic diseases, and neurological conditions.[4] Despite their therapeutic potential, conventional natural product drug discovery remains a complex and time-consuming process.[5] Traditional approaches involving extraction, isolation, structural characterization, and bioassay-guided fractionation often require extensive experimental effort and substantial financial investment.[6] Furthermore, many natural compounds exhibit poor bioavailability, low extraction yields, inconsistent chemical composition, and limited large-scale production, which hinder their successful clinical translation.

Recent advances in artificial intelligence (AI), machine learning (ML), deep learning (DL), multi-omics technologies, genome mining, and synthetic biology have significantly transformed the natural product drug discovery pipeline (show in fig 1).[7] AI-based approaches, including virtual screening, quantitative structure–activity relationship (QSAR)

modelling, molecular docking, and molecular dynamics simulations, enable rapid identification of bioactive compounds, prediction of therapeutic targets, and optimization of lead molecules.[8] At the same time, multi-omics technologies such as genomics, transcriptomics, proteomics, metabolomics, and microbiomics provide comprehensive insights into biosynthetic pathways, molecular mechanisms, and biomarker discovery, thereby improving the understanding of natural product biosynthesis and biological activity. Synthetic biology and metabolic engineering have further expanded the potential of natural products by enabling sustainable production through engineered microbial cell factories and CRISPR-based genome editing.[9] Combined with biotechnology, automation, and advanced computational tools, these interdisciplinary approaches have accelerated lead discovery, improved production efficiency, and enhanced the reproducibility of pharmaceutical research.

Although substantial progress has been achieved, several challenges remain, including variability of natural products, limited availability of standardized biological datasets, poor pharmacokinetic properties, algorithm interpretability, regulatory issues, and sustainability concerns. Addressing these challenges requires close collaboration among pharmacologists, biotechnologists, computational scientists, and regulatory agencies to facilitate efficient clinical translation. Despite these technological advances, integrating heterogeneous biological datasets with computational models remains a major challenge, highlighting the need for interdisciplinary approaches that combine experimental biology, computational science, and biotechnology.[10] This review summarizes recent advances in artificial intelligence, multi-omics technologies, genome mining, synthetic biology, and biotechnology in natural product drug discovery. It also discusses current challenges, emerging technologies, and future perspectives, highlighting how the integration of computational and experimental approaches can accelerate the development of safe, effective, and sustainable natural-product-derived therapeutics.

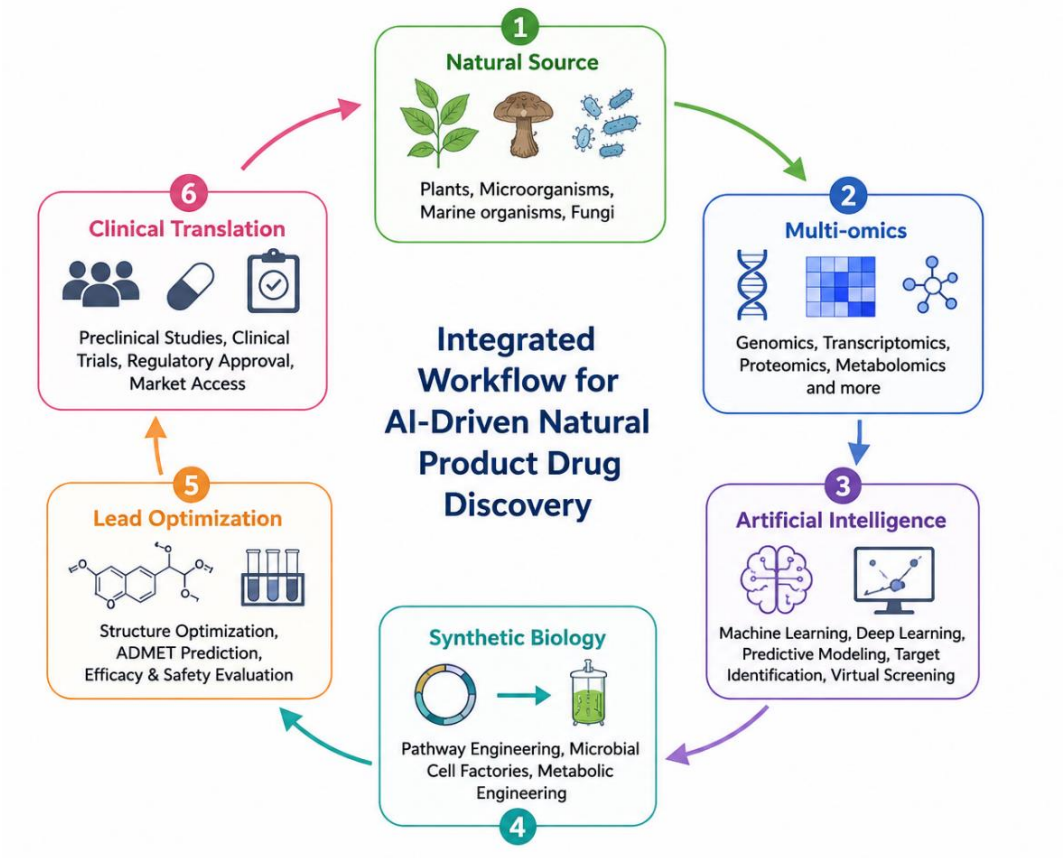

Fig. 1: Integrated Workflow for AI-Driven Natural Product Drug Discovery.

2. Historical Evolution of Natural Products in Medicine

The medicinal use of natural substances can be traced back thousands of years to early human civilizations that relied on plants, minerals, and animal-derived materials for therapeutic purposes.[11] Evidence suggests (show in table 1) that medicinal plants have been used since prehistoric times. Traditional medical systems including Ayurveda, Traditional Chinese Medicine, and Egyptian medicine extensively utilized natural substances for disease treatment.[12] These systems provided the foundation for modern pharmacognosy and natural-product-based drug discovery. The transition from traditional remedies to scientifically validated drugs occurred gradually with the isolation of active principles from medicinal plants.[13,14] The extraction of morphine from the opium poppy marked one of the earliest examples of isolating a pure bioactive compound from a natural source.[15] Similarly, the isolation of quinine from Cinchona bark revolutionized the treatment of malaria. The discovery of penicillin from a fungal source initiated the antibiotic era and demonstrated the enormous therapeutic potential of microbial metabolites. These landmark discoveries not only transformed clinical practice but also established natural products as credible and scientifically valuable sources of pharmaceutical agents. These early pharmacopoeias laid the

conceptual foundation for pharmacognosy and phytochemistry. The transition from traditional knowledge to evidence-based medicine continues to guide contemporary natural-product research and pharmaceutical innovation.[16]

Table 1: Landmark Natural Product-Derived Drugs and Their Therapeutic Applications.

Natural Source	Bioactive Compound	Drug/Class	Therapeutic Application	Mechanism of Action	Current Clinical Status
Papaver somniferum	Morphine	Opioid analgesic	Severe pain	μ-opioid receptor agonist	Approved
Cinchona spp.	Quinine	Antimalarial	Malaria	Inhibits heme detoxification	Approved
Taxus brevifolia	Paclitaxel	Anticancer	Breast, ovarian, lung cancers	Stabilizes microtubules	Approved
Artemisia annua	Artemisinin	Antimalarial	Malaria	ROS-mediated parasite killing	Approved
Catharanthus roseus	Vincristine	Anticancer	Leukemia, lymphoma	Microtubule inhibitor	Approved
Penicillium chrysogenum	Penicillin	Antibiotic	Bacterial infections	Cell wall synthesis inhibition	Approved
Tolypocladium inflatum	Cyclosporine	Immunosuppressant	Organ transplantation	Calcineurin inhibition	Approved
Marine sponge	Eribulin	Anticancer	Metastatic breast cancer	Microtubule dynamics inhibition	Approved

2.1 Terrestrial Plants as Sources of Bioactive Compounds

Terrestrial plants represent one of the most extensively studied reservoirs of bioactive secondary metabolites.[17] These compounds are synthesized primarily as defense mechanisms against herbivores, pathogens, and environmental stress. However, many of these secondary metabolites exert profound pharmacological effects in humans. Alkaloids constitute one of the most important classes of plant-derived compounds (show in table 2). These nitrogen-containing molecules often exhibit strong physiological effects due to their interaction with neurotransmitter receptors and ion channels.[18] For example, morphine, isolated from Papaver somniferum, acts as a μ-opioid receptor agonist and produces potent analgesic effects. Similarly, quinine, obtained from Cinchona species, interferes with the intraerythrocytic development of Plasmodium parasites and has historically served as an effective antimalarial agent.[19] Despite their immense diversity, natural sources often suffer

from variability in metabolite composition, seasonal fluctuations, and sustainability concerns, emphasizing the importance of modern computational and biotechnological approaches for efficient utilization. Numerous plant-derived alkaloids continue to provide valuable lead compounds for the development of novel therapeutic agents.[20]

Table 2: Major Sources of Natural Products and Representative Bioactive Compounds.

Source	Major Metabolites	Representative Examples	Therapeutic Applications
Terrestrial plants	Alkaloids, flavonoids, terpenoids	Morphine, Artemisinin, Paclitaxel	Cancer, diabetes, inflammation
Microorganisms	Antibiotics, peptides, polyketides	Penicillin, Streptomycin, Lovastatin	Infectious diseases
Marine organisms	Macrolides, alkaloids, peptides	Trabectedin, Ziconotide	Cancer, pain management
Animal-derived products	Venom peptides, enzymes	Hirudin, Captopril precursor	Cardiovascular disorders

Glycosides represent another significant group of plant metabolites. Cardiac glycosides such as digoxin exert their therapeutic action by inhibiting the sodium–potassium ATPase pump, thereby increasing intracellular calcium concentration and enhancing cardiac contractility.[21] Terpenoids, derived from isoprene units, display remarkable structural diversity and biological activity. Artemisinin, a sesquiterpene lactone containing an endoperoxide bridge, generates reactive oxygen species within malarial parasites, leading to their destruction.[22] Flavonoids, widely distributed polyphenolic compounds, possess antioxidant and anti-inflammatory properties and contribute to cardiovascular protection. The structural complexity and pharmacological versatility of plant-derived metabolites continue to inspire drug discovery programs aimed at identifying novel therapeutic agents.[23] Despite their therapeutic importance, plant-derived compounds face several limitations including low extraction yields, environmental variability, poor bioavailability, and challenges associated with standardization and large-scale production.[24]

2.2 Microorganisms in Drug Discovery

Microorganisms, particularly bacteria and fungi, have emerged as dominant contributors to modern drug development. Soil-dwelling actinomycetes and filamentous fungi are especially prolific producers of secondary metabolites with antimicrobial, immunosuppressive, and anticancer properties.[25, 26] The discovery of penicillin demonstrated that microorganisms

could produce compounds capable of selectively inhibiting pathogenic bacteria.[27] Subsequent identification of streptomycin, chloramphenicol, tetracycline, and numerous other antibiotics confirmed the immense pharmaceutical value of microbial metabolites. In addition to antibacterial agents, microorganisms have yielded cholesterol-lowering drugs such as statins, which inhibit HMG-CoA reductase and reduce cardiovascular risk.[28] Antiparasitic agents like avermectins have also been derived from microbial fermentation products. Advances in genomics and genome mining have revealed that many microorganisms possess silent biosynthetic gene clusters capable of producing previously unknown compounds.[29,30] By activating these gene clusters through genetic manipulation or environmental modification, researchers are uncovering novel molecules with promising therapeutic potential. Genome mining and bioinformatics-driven approaches have become powerful tools for identifying cryptic biosynthetic gene clusters, thereby accelerating the discovery of novel microbial natural products.[31,32]

2.3 Marine Organisms as Emerging Drug Sources

The marine environment represents one of the largest reservoirs of biodiversity on Earth, covering more than 70% of the planet's surface and harboring an immense diversity of organisms.[33] The unique ecological conditions present in marine ecosystems have driven the evolution of structurally diverse secondary metabolites with remarkable pharmacological potential.[34] Marine organisms inhabit extreme ecological niches characterized by high salinity, pressure variations, and intense competition, leading to the evolution of unique biochemical pathways. As a result, marine species synthesize structurally distinct secondary metabolites not typically found in terrestrial organisms.[35] Several marine-derived compounds have successfully transitioned into clinical use. Ziconotide, derived from cone snail venom, acts by blocking N-type calcium channels and provides potent analgesia without the addictive properties of opioids. Trabectedin, originally isolated from a tunicate, exerts anticancer activity by binding to the minor groove of DNA and disrupting transcription processes.[36] Eribulin, a synthetic analogue of a marine sponge metabolite, inhibits microtubule dynamics and is used in metastatic breast cancer treatment. Marine pharmacology continues to expand, supported by advancements in deep-sea exploration, marine microbiology, and sustainable harvesting techniques. Recent investigations have identified several marine-derived peptides, alkaloids, and polyketides exhibiting potent anticancer, antiviral, and anti-inflammatory activities, highlighting the immense pharmaceutical potential of marine biodiversity.[37]

Several marine-derived drugs, including trabectedin, eribulin, and ziconotide, have successfully reached clinical use, demonstrating the immense translational potential of marine biodiversity as a source of innovative therapeutics.[38,39]

2.4 Animal-Derived Bioactive Compounds

Animal-derived substances have also significantly contributed to therapeutic innovation.[40] Historically, hormones such as insulin were extracted from animal pancreases before recombinant DNA technology enabled large-scale production.[41] Anticoagulants like heparin are derived from animal tissues and remain widely used in clinical practice. Animal-derived bioactive compounds such as heparin from porcine tissues, albumin from bovine serum, lepirudin from medicinal leeches, and various venom-derived peptides possess remarkable therapeutic potential owing to their high target specificity.[42,43] The development of captopril was inspired by peptides isolated from snake venom that inhibit angiotensin-converting enzyme, thereby lowering blood pressure. Such examples highlight how animal-derived toxins can serve as templates for life-saving medications.[44]

3. Artificial Intelligence in Natural Product Drug Discovery

Artificial intelligence (AI) is increasingly being integrated into natural product research to facilitate lead identification, target prediction, toxicity assessment, and molecular optimization (show in table 3).[45,46] Machine learning algorithms can analyze large datasets of natural compounds and predict their biological activities with high accuracy.[47,48] AI-assisted virtual screening significantly reduces the time and cost associated with traditional drug discovery processes and has emerged as a promising approach for identifying novel therapeutic agents.[49–51] AI-based quantitative structure–activity relationship (QSAR) models are increasingly employed to predict biological activity, toxicity, and pharmacokinetic behavior of natural compounds.[52] These computational approaches facilitate rapid prioritization of promising candidates before experimental validation.[53] Furthermore, deep learning algorithms integrated with metabolomics, genomics, and cheminformatics datasets can identify novel biosynthetic pathways and predict previously unexplored bioactive molecules.[54] The combination of artificial intelligence and natural product research is expected to significantly accelerate future drug discovery programs. AI-assisted virtual screening has successfully identified novel antimicrobial compounds, including Halicin, using deep learning-based molecular prediction models.[51] Similarly, AlphaFold has improved protein structure prediction, facilitating target identification and enzyme

engineering for natural product biosynthesis. These examples demonstrate the practical impact of AI in accelerating natural product drug discovery.[52]

Table 3: Artificial Intelligence Applications in Natural Product Drug Discovery.

AI Technique	Major Application	Advantages	Limitations
Machine Learning	Bioactivity prediction	Rapid screening	Requires quality datasets
Deep Learning	Molecular property prediction	High accuracy	Black-box nature
Graph Neural Networks	Molecular representation	Better structural learning	Computationally intensive
Generative AI	De novo drug design	Novel scaffold generation	Experimental validation required
NLP	Literature mining	Knowledge extraction	Depends on text quality
Explainable AI	Model interpretation	Increased transparency	Still evolving

Despite remarkable progress, AI-based natural product drug discovery remains dependent on the availability of high-quality datasets. Many natural-product databases contain incomplete structural information, inconsistent biological annotations, and limited experimentally validated activity data. Furthermore, deep learning models often operate as black-box systems, reducing interpretability and limiting regulatory acceptance. Future research should prioritize explainable AI, standardized datasets, and experimental validation.[52,53]

3.1 AI Applications in Medicinal Plant Research

Recent pharmacognostic investigations have increasingly combined artificial intelligence with phytochemical and metabolomic datasets to prioritize bioactive constituents from medicinal plants (show in table 4). Machine learning models have been used to predict anti-inflammatory, antidiabetic, neuroprotective, and anticancer activities of flavonoids, alkaloids, and terpenoids before experimental validation. AI-assisted metabolite dereplication reduces repeated isolation of known compounds and accelerates the identification of novel phytochemicals. In addition, deep-learning approaches integrated with LC–MS and GC–MS data improve herbal authentication, quality control, and standardization of botanical preparations. These applications demonstrate that AI is not only a computational tool for drug discovery but also a practical technology for modern pharmacognosy.

Table 4: Conventional vs AI-assisted Pharmacognostic Workflow.

Step	Conventional	AI-assisted
Plant selection	Ethnobotany	Ethnobotany + data mining
Phytochemical screening	Wet-lab intensive	Metabolomics-guided
Bioactivity prediction	Experimental only	QSAR / ML prediction
Target identification	Time-consuming	Docking + network analysis
Standardization	Marker-based	Metabolomic fingerprinting

4. Multi-Omics Technologies in Natural Product Drug Discovery

4.1 Introduction to Multi-Omics

Multi-omics technologies have transformed natural product drug discovery, making it possible to study biological systems across multiple molecular layers simultaneously.[55] Traditional natural product research leaned heavily on phytochemical isolation and bioassay-guided fractionation. But these methods often fell short of giving a full picture of the molecular mechanisms behind how natural products are made and how they actually work pharmacologically.[56] Multi-omics, on the other hand, brings together genomics, transcriptomics, proteomics, metabolomics, lipidomics, microbiomics, epigenomics, and single-cell omics to build a systems-level picture of biological processes — helping researchers pinpoint new therapeutic targets and bioactive natural compounds.

Bringing these complementary datasets together offers a much clearer view into biosynthetic gene clusters, metabolic pathways, regulatory networks, enzyme functions, and cellular signaling. Paired with artificial intelligence, machine learning, and systems biology, multi-omics has sped up nearly every stage of natural-product drug development — from discovery and characterization to optimization and clinical translation. On top of that, progress in high-throughput sequencing, mass spectrometry, NMR spectroscopy, and computational biology has made these analyses more accurate, reproducible, and scalable than ever before.

Multi-omics approaches have become essential for finding new bioactive metabolites, understanding how plants defend themselves, uncovering microbial biosynthetic pathways, characterizing host-microbiome interactions, and identifying disease-related molecular signatures. As a result, these technologies now sit at the core of precision pharmacognosy and next-generation natural product drug discovery.[55]

4.2 Genomics

Genomics looks at an organism's complete genetic makeup and forms the foundation for understanding how natural products are biosynthesized. Whole-genome sequencing has

allowed researchers to pinpoint biosynthetic gene clusters (BGCs) responsible for producing alkaloids, terpenoids, polyketides, flavonoids, peptides, and many other secondary metabolites. By sequencing the genomes of medicinal plants, fungi, bacteria, and marine organisms, scientists have massively expanded the pool of potential drug candidates, uncovering biosynthetic pathways that were previously unknown.

Genome mining has emerged as one of the most powerful genomic strategies in pharmaceutical research. Tools like AntiSMASH, PRISM, BAGEL, and DeepBGC let researchers computationally spot cryptic biosynthetic gene clusters — the ones that stay transcriptionally silent under normal lab conditions. Artificial intelligence takes this further, predicting gene functions, enzyme activities, metabolite structures, and biosynthetic relationships with impressive accuracy.[56]

Comparative genomics helps identify conserved biosynthetic pathways across related species and supports evolutionary analysis of secondary metabolism. Functional genomics, CRISPR-Cas genome editing, and transcriptome-guided genome annotation have added further insight into the regulatory mechanisms that control natural product biosynthesis.[57]

4.3 Metabolomics

Metabolomics has become one of the most influential omics technologies in natural product drug discovery, largely because metabolites are the final functional output of cellular metabolism. Profiling these metabolites gives direct insight into the chemical diversity that drives biological activity and therapeutic efficacy.[58]

Advanced analytical platforms — including LC-MS/MS, GC-MS, CE-MS, UPLC-QTOF-MS, Orbitrap mass spectrometry, Fourier-transform ion cyclotron resonance (FT-ICR), and nuclear magnetic resonance spectroscopy — can identify and quantify thousands of metabolites within complex biological samples at once.[59]

Untargeted metabolomics helps uncover previously unknown bioactive compounds, while targeted metabolomics focuses on the quantitative analysis of specific therapeutic metabolites. AI-assisted metabolomics has considerably improved spectral annotation, metabolite identification, dereplication, molecular networking, and biomarker discovery.

Metabolomics has also proven invaluable for quality control of herbal medicines, authenticating medicinal plants, standardizing botanical extracts, and evaluating pharmacological responses during preclinical and clinical studies.[60]

Metabolomic fingerprinting has become a powerful tool for the standardization and quality assessment of herbal medicines. LC–MS and NMR-based metabolic profiling can distinguish authentic medicinal plants from adulterants, identify geographical and seasonal variations, and establish reproducible chemical fingerprints for botanical extracts. Integration of chemometric analysis with AI algorithms further enhances classification accuracy and supports regulatory quality control of herbal formulations.

4.4 Multi-Omics Data Integration

Individual omics technologies provide valuable biological information; however, integration of multiple datasets offers significantly greater insight into complex biological systems. Multi-omics integration combines genomic, transcriptomic, proteomic, metabolomic, and phenotypic information to construct comprehensive molecular interaction networks.

Artificial intelligence, network pharmacology, Bayesian modeling, graph neural networks, and systems biology facilitate integration of heterogeneous omics datasets and prediction of biological pathways responsible for disease development and therapeutic responses.[57]

Multi-omics integration has accelerated biomarker discovery, target identification, drug repurposing, precision medicine, systems pharmacology, and natural product optimization. These integrated approaches represent one of the most promising strategies for future pharmaceutical research.

Collectively, multi-omics technologies provide complementary information regarding gene expression, protein regulation, metabolite biosynthesis, lipid metabolism, and microbial interactions. Integration of these datasets enables a systems-level understanding of natural product biosynthesis and significantly enhances AI-assisted drug discovery.[61]

5. Synthetic Biology in Natural Product Drug Discovery

Synthetic biology is an interdisciplinary field combining molecular biology, metabolic engineering, systems biology, computational biology, biotechnology, and engineering principles to redesign biological systems for the production of valuable compounds. Within natural product drug discovery, synthetic biology has emerged as one of the most

transformative technologies by enabling sustainable production of complex bioactive metabolites that are otherwise difficult to obtain from natural source.[62]

Many clinically important natural products occur in extremely low concentrations, require slow-growing organisms, or originate from endangered plant and marine species. Synthetic biology overcomes these limitations through rational engineering of microbial cell factories capable of producing high-value natural compounds at industrial scale.

5.1 Biosynthetic Gene Cluster Engineering

Natural product biosynthesis is governed by biosynthetic gene clusters encoding enzymes responsible for sequential assembly of complex metabolites. Advances in genome sequencing and bioinformatics have enabled identification of thousands of biosynthetic gene clusters within bacteria, fungi, medicinal plants, and marine organisms.[62]

Synthetic biology enables reconstruction, optimization, and heterologous expression of these gene clusters in genetically engineered microorganisms including *Escherichia coli*, *Saccharomyces cerevisiae*, *Bacillus subtilis*, and *Streptomyces* species. Such approaches substantially improve metabolite yield while enabling production of novel structural analogues through pathway engineering.

5.2 CRISPR-Cas Genome Editing

CRISPR-Cas technology has transformed synthetic biology, giving researchers precise control over genetic modification in microorganisms and medicinal plants. It's used to delete competing pathways, activate silent biosynthetic gene clusters, insert heterologous biosynthetic pathways, engineer promoters, and regulate gene expression.

CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) go a step further, allowing programmable control over metabolic networks without making permanent changes to the genome. Together, these tools have sped up the development of engineered strains for pharmaceutical production.[63]

5.3 Microbial Cell Factories

Engineered microorganisms now serve as sustainable production platforms for a wide range of natural products — including artemisinin precursors, taxol intermediates, opioids, cannabinoids, flavonoids, carotenoids, alkaloids, terpenoids, and antimicrobial peptides.[64]

Yeast, bacteria, filamentous fungi, and cyanobacteria have all been engineered to produce valuable metabolites with better productivity, scalability, and environmental sustainability. Ongoing advances in fermentation technology, systems biology, and computational optimization keep pushing industrial biomanufacturing forward.[65]

5.4 Artificial Intelligence in Synthetic Biology

Artificial intelligence has become a core part of synthetic biology. Machine learning algorithms now predict enzyme specificity, protein folding, metabolic flux distribution, pathway efficiency, promoter strength, codon optimization, and fermentation conditions.

Deep learning models are also helping with protein engineering, enzyme evolution, metabolic pathway reconstruction, biosynthetic network analysis, and automated strain design.[66]

Synthetic biology still faces real challenges despite its progress in sustainable natural product production — metabolic burden, pathway instability, low product yields, regulatory hurdles, and scaling up for industrial use all remain obstacles. Continued progress in metabolic engineering, AI-assisted pathway optimization, and fermentation technology should help address these limitations over time.[67]

6. Role of Biotechnology and Modern Technologies

Recent advances in biotechnology have reshaped natural product drug discovery, bringing molecular biology, genetic engineering, computational science, and advanced analytical tools into what was traditionally pharmacognostic research. In the past, discovering natural-product-derived therapeutics relied on bioassay-guided fractionation, phytochemical isolation, and extensive biological testing — a process that was often slow and labor-intensive.[68]

Modern biotechnological approaches have speed things up considerably, making it possible to identify, characterize, optimize, and sustainably produce bioactive compounds much faster than before (The integrated workflow is illustrated in Fig 2.). Genome editing tools, CRISPR-Cas systems especially, have made it far easier to manipulate the biosynthetic pathways behind secondary metabolite production. These tools can activate silent biosynthetic gene clusters, boost metabolite yields, and support the development of engineered microorganisms capable of producing valuable natural products.[69]

High-throughput screening (HTS) and high-content screening (HCS) platforms have likewise sped up lead compound identification, allowing thousands of natural products to be evaluated automatically with greater speed, sensitivity, and reproducibility.[70]

Emerging microfluidic technologies including organ-on-a-chip and lab-on-a-chip systems offer physiologically relevant platforms for testing the efficacy, toxicity, and pharmacokinetics of natural compounds, cutting down on the need for conventional animal models. These systems improve preclinical drug evaluation and open the door to more personalized therapeutic research. Alongside this, laboratory automation and robotic platforms have made experiments more reproducible, reduced human error, and boosted research output by handling repetitive lab procedures with high precision.

Digital technologies are reshaping pharmaceutical research too. AI-assisted lab automation, digital twins, cloud computing, and IoT-based monitoring now allow real-time analysis of biological data, fine-tuning of experimental conditions, and predictive modeling of biosynthetic pathways supporting data-driven decisions throughout drug discovery while cutting both time and cost.

Nanobiotechnology has become an effective way to tackle the poor solubility, limited bioavailability, and rapid metabolism that affect many natural compounds. Nanoscale drug delivery systems can improve therapeutic outcomes through controlled release, better stability, and targeted delivery. On top of this, environmentally sustainable methods plant tissue culture, microbial fermentation, metabolic engineering, precision fermentation, and green extraction help ensure reliable natural product production while protecting biodiversity and minimizing ecological impact.

Altogether, combining biotechnology with AI, multi-omics, synthetic biology, automation, and nanotechnology has created a modern, multidisciplinary framework for natural product drug discovery. These innovations speed up the identification and optimization of new therapeutic candidates, while also supporting sustainable production, precision medicine, and efficient clinical translation. Table 5 summarizes the major biotechnological tools and their applications in natural product drug discovery.

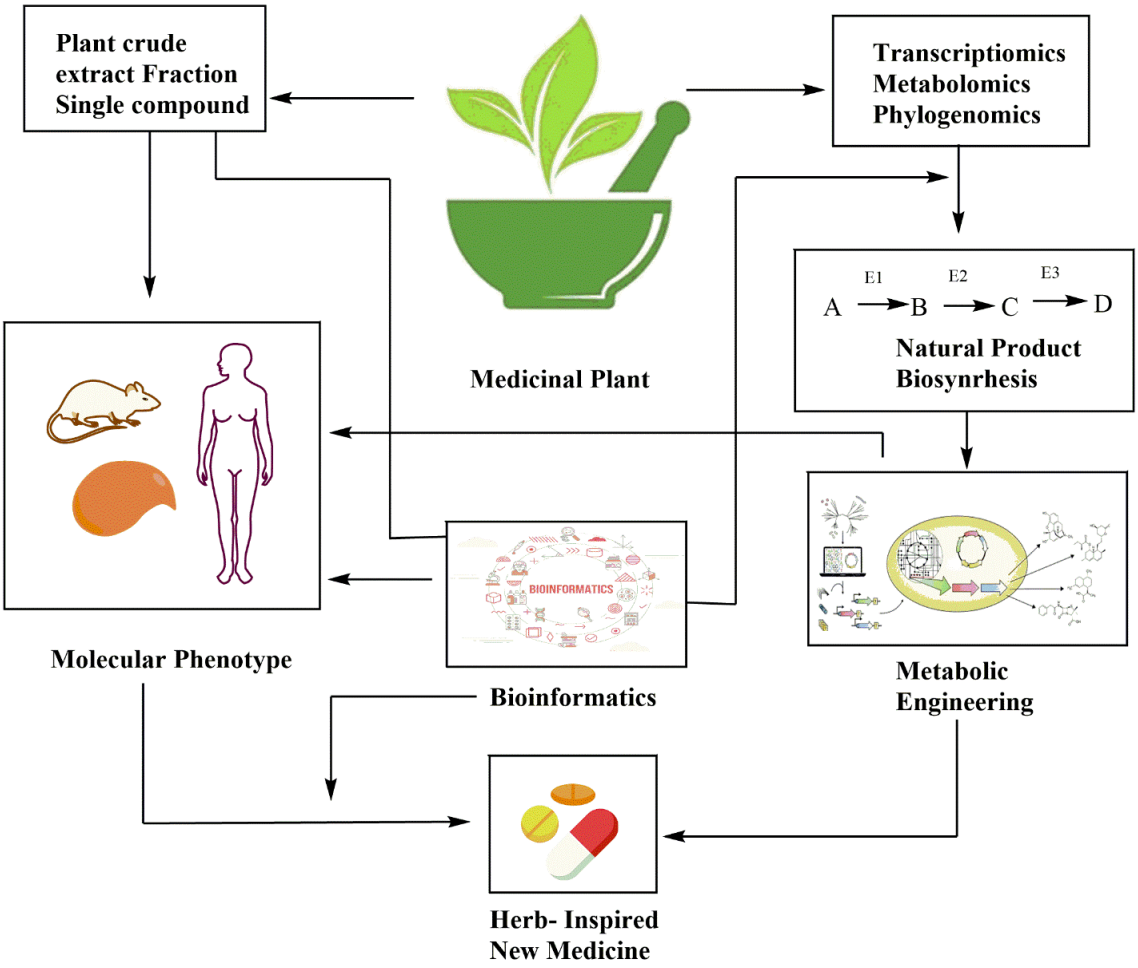

Fig. 2: From Medicinal Plant to AI-Optimized Therapeutic.

Table 5: Modern Technologies Used in Natural Product Drug Discovery.

Technology	Principle	Application in Natural Product Research
Genomics	Analysis of genetic information	Identification of biosynthetic gene clusters
Metabolomics	Study of metabolic profiles	Detection of bioactive metabolites
Proteomics	Protein expression analysis	Understanding mechanism of action
High-Throughput Screening	Rapid biological screening	Identification of active compounds
Synthetic Biology	Engineering biosynthetic pathways	Production of natural products
Artificial Intelligence	Computational prediction models	Drug discovery and lead optimization
Molecular Docking	In silico interaction study	Target-based drug design

7. Current Challenges and Limitations

Despite real progress in artificial intelligence, multi-omics, synthetic biology, and biotechnology, several scientific, technological, and regulatory hurdles still stand in the way of translating natural products into clinically approved therapeutics. One of the biggest obstacles is just how complex and variable natural products are. The chemical makeup of medicinal plants and other natural sources depends on genetic factors, geography, climate, harvesting season, cultivation practices, and post-harvest processing all of which lead to significant batch-to-batch variability and make standardization difficult. This variability often hurts reproducibility and complicates quality control during pharmaceutical development.[71]

Another major challenge is the shortage of high-quality, standardized biological datasets needed for advanced computational analysis. AI has sped up target prediction, virtual screening, and lead optimization considerably, but its performance still depends heavily on the quality, diversity, and completeness of the data it's trained on. Incomplete chemical databases, inconsistent biological annotations, data imbalance, and insufficient experimental validation all tend to weaken the predictive accuracy and generalizability of machine learning algorithms. On top of that, many advanced AI models function as "black boxes" hard to interpret, which makes researchers and regulatory agencies understandably cautious about trusting them.

Integrating multi-omics datasets brings its own set of computational challenges. Genomic, transcriptomic, proteomic, metabolomic, and microbiome data are typically generated on different platforms using different protocols, which makes harmonizing, normalizing, and interpreting them genuinely complex. Doing this well requires advanced bioinformatics pipelines, high-performance computing infrastructure, and interdisciplinary expertise resources that aren't readily available at many research institutions.[55]

From a pharmaceutical standpoint, many natural compounds struggle with poor aqueous solubility, low oral bioavailability, rapid metabolism, limited stability, and nonspecific tissue distribution, all of which limit their clinical usefulness. Nanotechnology and advanced drug delivery systems have helped address some of these issues, but large-scale manufacturing, long-term stability, and regulatory approval remain difficult hurdles. Likewise, synthetic biology and metabolic engineering now make sustainable production of valuable metabolites possible but pathway complexity, genetic instability, low yields, and high production costs still stand in the way of commercial-scale implementation.[72]

Ethical, environmental, and regulatory issues add further complications to natural product drug development. Overharvesting medicinal plants, marine organisms, and other biological resources threatens biodiversity and ecological sustainability. Regulatory agencies, meanwhile, demand rigorous evidence of safety, efficacy, quality, and manufacturing consistency before approving natural-product-derived therapeutics. And without harmonized international regulatory guidelines combined with intellectual property concerns and limited clinical evidence product commercialization tends to face further delays.[73]

Overcoming these challenges will take coordinated effort across disciplines pharmacologists, computational scientists, biotechnologists, chemists, clinicians, regulatory authorities, and industry partners all have a role to play. Progress in data standardization, explainable AI, sustainable biomanufacturing, advanced analytical technologies, and international regulatory harmonization will all be essential to fully realizing the therapeutic potential of natural products.[73]

8. Future Perspectives

Future directions in natural product drug discovery are expected to be defined by the convergence of artificial intelligence (AI), multi-omics technologies, synthetic biology, biotechnology, and precision medicine. Rather than functioning as independent domains, these disciplines are increasingly being integrated into unified discovery platforms capable of rapid identification of bioactive compounds, prediction of therapeutic targets, optimization of lead molecules, and support of sustainable biopharmaceutical production. Such convergence has the potential to shorten development timelines, reduce research expenditure, and improve translational and clinical success. Artificial intelligence is progressing beyond conventional predictive modeling toward explainable AI, generative AI, foundation models, and autonomous research systems. These computational approaches can enhance the interpretability of decision-making processes and facilitate automated hypothesis generation, de novo molecular design, and optimization of natural-product-derived scaffolds. Integration with robotics and self-driving laboratories may enable closed-loop Design-Build-Test-Learn workflows, accelerating experimental validation and lead refinement with limited manual intervention. Advances in multi-omics and single-cell technologies are expected to provide deeper mechanistic insights into disease pathogenesis, biosynthetic networks, host–microbiome interactions, and interindividual variability in therapeutic response. The integration of genomics, transcriptomics, proteomics, metabolomics, epigenomics, and

microbiomics can support biomarker discovery, precision phytotherapy, and individualized pharmacological interventions, thereby improving patient stratification and minimizing adverse effects. Synthetic biology and metabolic engineering are likely to become central components of sustainable natural product production. Engineered microbial cell factories, precision fermentation systems, cell-free biosynthesis, and programmable biosynthetic pathways can decrease dependence on threatened biological resources while enabling scalable and environmentally responsible manufacturing. Green extraction technologies, circular bioeconomy models, and renewable bioprocessing strategies are expected to reinforce the sustainability of future production systems. Emerging technologies including digital twins, organ-on-a-chip platforms, quantum computing, cloud-based laboratories, advanced nanomedicine, and real-time biosensing are also positioned to transform the field. These approaches may improve therapeutic outcome prediction, optimize targeted drug delivery, strengthen preclinical modeling, and facilitate patient-specific treatment strategies. Progress in this area will require standardized databases, interoperable bioinformatics infrastructures, rigorous validation frameworks, and internationally harmonized regulatory policies to support efficient clinical translation. Translation of these technological advances into clinically effective therapies depends on coordinated interaction among computational scientists, molecular biologists, chemists, pharmacologists, clinicians, and regulatory authorities. Interdisciplinary integration therefore represents a fundamental requirement for converting emerging scientific innovations into safe, effective, and accessible natural-product-based therapeutics.

9. CONCLUSION

Natural products remain indispensable sources of chemically diverse therapeutic leads. The integration of artificial intelligence with genomics, metabolomics, and modern biotechnological tools is transforming contemporary pharmacognosy by accelerating phytochemical prioritization, target prediction, herbal standardization, and sustainable production of bioactive metabolites. Among these approaches, metabolomics-guided standardization and AI-assisted bioactivity prediction appear particularly promising for improving the reproducibility and translational value of herbal medicines. Nevertheless, successful clinical application will require high-quality datasets, explainable computational models, rigorous experimental validation, and harmonized regulatory standards. Continued collaboration between pharmacognosists, phytochemists, computational scientists, and pharmacologists will be essential for translating these technological advances into safe,

effective, and standardized herbal therapeutics.

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There is no Conflict of interest

List of Abbreviation

Abbreviation	Full Form
AI	Artificial Intelligence
ML	Machine Learning
DL	Deep Learning
NLP	Natural Language Processing
QSAR	Quantitative Structure–Activity Relationship
GNN	Graph Neural Network
XAI	Explainable Artificial Intelligence
NP	Natural Product
NPs	Natural Products
BGC	Biosynthetic Gene Cluster
BGCs	Biosynthetic Gene Clusters
DBTL	Design–Build–Test–Learn
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRISPR-Cas	Clustered Regularly Interspaced Short Palindromic Repeats–CRISPR-associated Protein
CRISPRi	CRISPR Interference
CRISPRa	CRISPR Activation
RNA	Ribonucleic Acid
RNA-Seq	RNA Sequencing
DNA	Deoxyribonucleic Acid
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry

Abbreviation	Full Form
LC-MS	Liquid Chromatography–Mass Spectrometry
GC-MS	Gas Chromatography–Mass Spectrometry
CE-MS	Capillary Electrophoresis–Mass Spectrometry
UPLC-QTOF-MS	Ultra-Performance Liquid Chromatography–Quadrupole Time-of-Flight Mass Spectrometry
MALDI-TOF-MS	Matrix-Assisted Laser Desorption/Ionization–Time-of-Flight Mass Spectrometry
FT-ICR	Fourier Transform Ion Cyclotron Resonance
NMR	Nuclear Magnetic Resonance
HTS	High-Throughput Screening
HCS	High-Content Screening
IoT	Internet of Things
ROS	Reactive Oxygen Species
ATP	Adenosine Triphosphate
HMG-CoA	3-Hydroxy-3-Methylglutaryl Coenzyme A
ACE	Angiotensin-Converting Enzyme
BSL	Biosafety Level *(if mentioned in future revisions)*
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
PK	Pharmacokinetics
PD	Pharmacodynamics
omics	Comprehensive Biological Data Analysis Technologies
Genomics	Genome-wide Study of DNA
Transcriptomics	Genome-wide Study of RNA Transcripts
Proteomics	Large-scale Study of Proteins
Metabolomics	Comprehensive Study of Metabolites
Lipidomics	Large-scale Study of Lipids
Microbiomics	Study of Microbial Communities
Epigenomics	Genome-wide Study of Epigenetic Modifications

Abbreviation	Full Form
In silico	Computer-based Computational Analysis
DB	Database

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