Artificial intelligence-driven metabolic engineering is applied to the development of active ingredients in Traditional Chinese Medicine

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Abstract: Metabolic engineering serves as a pivotal component in establishing microbial platforms for the effective biosynthesis of expensive compounds, therapeutic agents, and vegetative production systems. This field necessitates thorough comprehension of intracellular biochemical networks (encompassing molecular transformation routes and corresponding catalytic proteins). Nevertheless, the biochemical routes and critical catalysts that control numerous high-value target molecules have not been fully characterized, which is the main bottleneck for the heterologous synthesis of high-value chemicals. To address this limitation, scientists have devised optimized production circuits through the engineering of artificial biocatalysts and de novo biochemical reaction sequences. With the continuous accumulation of biological big data, the data-driven methods of artificial intelligence (AI) technology are promoting the further development of protein and metabolic pathway design. In this paper, we introduce AI-driven machine learning algorithms in prediction models, and also review recent research progress on AI-assisted metabolic engineering design and production of high-value compounds, focusing on how to use AI methods to achieve directed evolution of strains.

1 Introduction

Metabolic engineering mainly involves the optimization of biosynthetic pathways to produce specific compounds. However, the yield and extraction rate of many high-value natural compounds. This not only limits the wide application of these compounds, but also increases production costs. Similarly, in the traditional fermentation process, some microorganisms have low utilization efficiency of substrates, or insufficient activity of key enzymes in the metabolic pathway, resulting in limited accumulation of target compounds. In recent years, the application of AI technology in metabolic engineering has provided new ideas for solving these problems.

With the rise of deep learning and large-scale pre trained models, artificial intelligence technology has been widely applied in fields such as genomics, single-cell genomics, cancer biology, etc. It not only accelerates the speed of data processing and analysis, but also provides new perspectives for revealing biological complexity. Metabolic engineering can improve the yield and quality of natural active ingredients by optimizing biosynthetic pathways and the metabolic capacity of host cells. Artificial intelligence technology can accurately predict and optimize metabolic networks through deep learning and machine learning algorithms, and combining the two can further improve bioavailability.

In addition, AI can also be combined with high-throughput screening technology to quickly identify and optimize compounds with special pharmacological activities. Integrating these methodologies is anticipated to not fail in overcoming the limitations associated with poor pharmaceutical accessibility intrinsic to nature-derived molecules, while offering enhanced efficacy and target-specific interventions for pathological conditions. In this review, we focus on the development and application of artificial intelligence combined with metabolic engineering in the development of active molecules in medicinal plants.

2 Metabolic Engineering and Development of Active Ingredients in Traditional Chinese Medicine

2.1 Optimization requirements for metabolic pathways of active ingredients in traditional Chinese medicine

The pharmacological active ingredients of herbal derived drugs have important scientific value in contemporary pharmacological exploration, but the analysis of their biosynthetic pathways and large-scale production still face technical challenges. Many active ingredients in traditional Chinese medicine come from rare species, and their biosynthetic pathways are not fully understood, which limits their widespread application. To overcome these limitations, metabolic engineering and synthetic

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biology techniques have been combined with ethnopharmacology to improve the yield of target components by optimizing metabolic pathways. For example, by introducing the ginsenoside synthesis pathway into yeast and optimizing key enzyme expression, its yield was significantly increased [1]. In addition, the use of metabolomics and network pharmacology techniques, combined with AI analysis, can deeply analyze the mechanism of action of traditional Chinese medicine compounds and provide theoretical support for the optimization of metabolic pathways [2].

Artificial intelligence technology has shown great potential in optimizing the metabolic pathways of active ingredients in traditional Chinese medicine. Machine learning algorithms can identify key molecular connections in biochemical transformation networks through multidimensional mining of bioinformatics datasets, thereby optimizing biocatalytic performance. These methods can also systematically characterize the biotransformation kinetics of herbal derived therapies in mammals, providing theoretical support for optimizing metabolic pathways. For example, the metabolic changes of the key component rosin aldehyde (CFA) in Eucommia ulmoides bark can be optimized through AI analysis for its extraction and production process [3].

In summary, artificial intelligence technology has brought new breakthroughs in optimizing the metabolic pathways of active ingredients in traditional Chinese medicine. The machine learning driven biosynthetic network optimization strategy not only improves the production efficiency of bioactive plant chemicals, but also reveals the therapeutic mechanism at the molecular level, providing a powerful technical framework for evidence-based improvement of plant derived drugs.

2.2 Challenges Faced by Traditional Metabolic Engineering

First of all, the resources inside the host cells are limited. When exogenous genes or metabolic pathways are introduced to produce unnatural products, there will be competition between exogenous elements and the survival needs of the cells themselves. Cells tend to give priority to their own growth and reproduction needs, while ignoring the expression of foreign genes, resulting in low yield of target products. The expression of exogenous genes in host cells may be unstable and easily affected by the intracellular environment, resulting in low efficiency in the production of specific substances. The metabolic network of cells is extremely complex. Natural cells have evolved over a long period of time, including thousands of enzyme genes and complex regulatory mechanisms. Only a few genes in the pathway from raw materials to product synthesis are modified, and in many cases, the expected results cannot be achieved.

Secondly, traditional metabolic engineering often relies on isolated modification of specific enzymes or metabolic nodes. This method can easily lead to frequent imbalance of cell metabolic flow, and it is difficult to optimize the overall metabolic efficiency. Static regulation methods (such as knockout of competitive pathways and overexpression of rate-limiting enzymes) may also lead to metabolic imbalance between cell growth and product synthesis, thereby reducing the synthesis efficiency of target products. When implementing engineered genome modifications to synthesize extrinsic biogenic substances, microorganisms frequently manifest distinct autoregulatory resistance mechanisms. This phenomenon specifically encapsulates the intrinsic biological prioritization of homeostatic equilibrium maintenance over exogenous compound biosynthesis, thereby achieving suboptimal production efficiency of desired metabolites through self-preservation biochemical strategies.

These phenomena undeniably reveal that conventional organismal metabolic intervention approaches cannot be considered fully adequate for reconfiguring interrelated regulatory networks. Persistent constraints remain particularly evident in refining catalytic equilibrium states of complex enzymatic cascades and driving economically viable synthesis trajectories for specialized bioactive molecules.

3 Key technologies of artificial intelligence

Metabolic engineering mainly involves the optimization of biosynthetic pathways to produce specific compounds. However, many active ingredients of traditional Chinese medicine, such as artemisinic acid, glycyrrhizic acid, etc., usually have complex chemical structures, which makes traditional metabolic engineering methods less efficient. In recent years, the combination of artificial intelligence (AI) technology and metabolic engineering has provided new solutions to this problem. AI can assist metabolic engineering in a variety of ways, especially in the development of active molecules in medicinal plants. For example, AI-driven machine learning algorithms can optimize gene expression intensity and regulatory elements in metabolic pathways, thereby increasing the yield of target compounds [4]. In addition, AI can further optimize the metabolic network by predicting enzyme activity and metabolic flux. In practical applications, AI technology can be used to design and optimize microbial production systems. For example, through deep learning models, researchers can predict and adjust key nodes in metabolic pathways, thereby increasing the yield of active ingredients in traditional Chinese medicine. AI can also combine metabolomics data to deeply analyze the changes of metabolites and further optimize metabolic engineering strategies. In addition, the combination of AI and metabolic engineering can also accelerate the process of drug development. By simulating the metabolic network and predicting the efficiency of the biosynthetic pathway, AI can quickly screen out the optimal metabolic modification scheme and reduce the experimental cost and time. This collaborative innovation not only improves the efficiency of metabolic engineering, but also provides a more powerful tool for the development of new drugs.

3.1 AI driven machine learning algorithms

In metabolic engineering, AI-driven machine learning algorithms provide powerful tools for the optimization of complex biosynthetic pathways by constructing data-driven models. For example, machine learning algorithms can integrate multi-dimensional data such as genome, transcriptome, and metabolomics to construct a genome-scale metabolic model (GEM), and combine constrained optimization techniques to systematically describe and simulate metabolic processes in organisms [4]. This method can not only identify the key nodes and bottlenecks in the metabolic pathway, but also guide the experimental design of metabolic engineering by predicting gene modification and metabolic flow. Machine learning algorithms are mainly divided into three categories: supervised learning, unsupervised learning and reinforcement learning. In this section, we focus on the basic knowledge of machine learning algorithms, which are divided into two categories (unsupervised and supervised).

3.1.1 Supervised Learning

Supervised learning is one of the most common methods in machine learning, which constructs a mapping function between features and labels by labeling datasets (X, y) to achieve classification or regression prediction of new input data. Its main tasks include regression (predicting continuous values such as house prices or metabolite concentrations) and classification (predicting discrete categories such as spam recognition or image object detection). The advantages of supervised learning lie in clear learning objectives, structured training processes, and the ability to optimize parameters through large-scale annotated data, covering a wide range of algorithms from linear models (such as linear regression, logistic regression) to nonlinear models (such as decision trees, support vector machines, neural networks). However, its limitations lie in relying on labeled data, obtaining high-quality labeled data may be time-consuming and costly, and model performance and generalization ability are affected by the quality and diversity of training data.

Despite its limitations, supervised learning remains one of the most widely used techniques in machine learning, achieving significant results in fields such as biomedical research, drug development, financial risk prediction, image recognition, and natural language processing. In metabolic engineering, supervised learning can be used to optimize metabolic pathways, predict enzyme activity, design gene editing strategies, and construct metabolic network models, providing powerful tools for the analysis and optimization of complex biological systems.

3.1.2 Unsupervised Learning

Unsupervised learning is a key method in machine learning that focuses on automatically discovering hidden structures, patterns, or relationships from unlabeled data. Unlike supervised learning, it does not require pre-defined labels or target values, but learns and analyzes based on the characteristics and internal rules of the data itself. This method is particularly suitable for processing complex, high-dimensional, and unlabeled datasets, which can help researchers explore the basic features of the data, discover potential rules, and provide support for subsequent analysis and decision-making. Its main tasks include clustering (dividing data into clusters with high similarity), dimensionality reduction (extracting key information, simplifying data structure), anomaly detection (identifying outliers), and association rule mining (discovering frequent patterns).

Unsupervised learning has a wide range of applications in multiple fields. For example, in the biomedical field, it can be used to analyze gene expression data, discover clusters of different gene expression patterns, and reveal potential biological mechanisms; In metabolic engineering, it can be used to analyze metabolite concentration data.

4 Key Technology Applications of Machine Learning in Metabolic Engineering

In recent years, with the continuous development of AI technology, it has a very wide range of applications in biotechnology. It can integrate multi-dimensional data such as genome, transcriptome, and metabolomics to construct a genome-scale metabolic model (GEM), and combine constrained optimization techniques to systematically describe and simulate metabolic processes in organisms [5]. The integration of high-throughput omics analytics and computational modeling optimizes critical bioprocess components including enzymatic engineering, predictive refinement of biochemical pathways, and dynamic monitoring of biosynthesis workflows. This methodological advancement not only enhances the bioindustrial yield of anti-inflammatory agents through rational strain design but also reduces developmental expenditure, creating enabling technological frameworks for next-generation precision pharmaceutics (Figure 1).

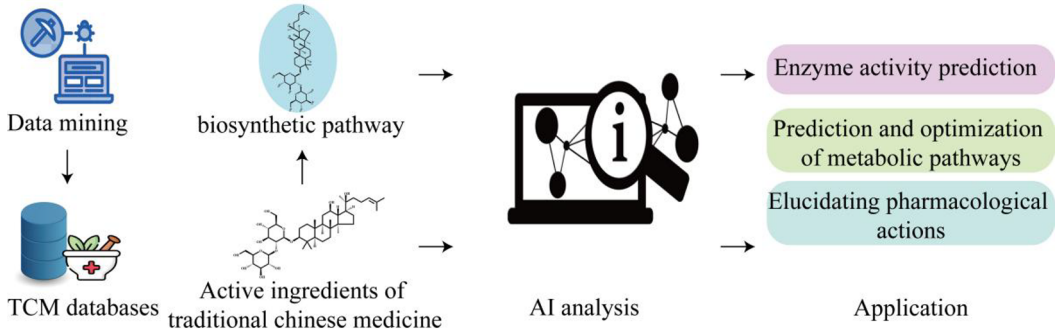

Figure 1. The implementation of machine learning-driven analytical platforms for multi-component botanical therapeutics enables systematic characterization, innovative screening, and multi-target mechanistic validation of phytochemical constituents. This computational pharmacology paradigm facilitates rigorous elucidation of natural product bioactivity through intelligent algorithm frameworks.

4.1 Pathway Prediction

The application of artificial intelligence in predicting drug metabolism pathways is becoming an important tool in the field of drug development. Through machine learning and deep learning techniques, it is possible to effectively predict the metabolic pathways of small molecule drugs, thereby accelerating drug discovery and design.

AISMPred is a machine learning based anti-inflammatory small molecule (AISMs) [6] prediction tool that integrates compound information and multiple molecular descriptors from the PubChem BioAssay database. This method uses classifiers such as Random Forest (RF) and Extra Tree (ET) to construct the model. In independent testing, the ET model achieved an accuracy of 92% when combined with a mixed feature set, with an AUC value of 0.97, demonstrating strong predictive ability. Deep Neural Networks (DNNs) have demonstrated significant utility in predicting anti-inflammatory drug metabolic pathways, particularly for sesquiterpene biosynthesis in engineered yeast (Saccharomyces cerevisiae). Zhang et al. [7] leveraged DNN-guided pathway optimization to develop an orthogonal peroxisomal protein transport system, enabling targeted enzyme localization. This AI-driven approach, coupled with high-throughput screening, enhanced α-humulene (a monocyclic sesquiterpene) production to 17.33 g/L in 5-L fermenters while refining peroxisome dynamics. In addition, artificial intelligence technology has also made progress in the prediction of drug target binding affinity. Through the combination of graph neural network (GNN) and self-attention mechanism, it is possible to more accurately predict the interactions between drugs and targets [8]. In addition, deep learning techniques have been used to predict the metabolic pathways of anti-inflammatory small molecules. For example, the AIPs-DeepEnC-GA model [9] achieves high-precision prediction of anti-inflammatory peptides (AIPs) by combining a variety of deep learning architectures (such as DNN, convolutional neural network CNN, recurrent neural network RNN, etc.) and using genetic algorithms for feature selection and model optimization. The model achieves a prediction accuracy of 94.39 % and an AUC value of 0.98 on the training data set, showing strong prediction ability.

These applications not only improve the efficiency of anti-inflammatory drug development, but also provide new possibilities for personalized medicine and precision medicine. Through artificial intelligence-driven metabolic pathway prediction, researchers can better understand the mechanism of drug action, optimize drug design, and reduce the failure rate in clinical trials.

4.2 Enzyme activity prediction and modification

Artificial intelligence has emerged as a pivotal technology in enzyme engineering, particularly for activity prediction and catalytic modification. The DeepMind-developed AlphaFold2 exemplifies this progress, revolutionizing structural biology by accurately predicting protein 3D architectures from amino acid sequences at atomic-level precision, thereby establishing new computational paradigms for enzyme design. In 2022, Yao et al. [10] used alphafold2 to predict the model of Pq3-O-UGT2 enzyme, and improved its catalytic efficiency through semi rational design and site mutation. Combined with molecular biology methods, the final yield of ginsenoside Rg3 by shake flask fermentation reached 83.6 mg/L (dry weight of 7.0 mg/g).

Recent advancements in AI-driven enzyme engineering demonstrate transformative potential across computational design and adaptive evolution. Utilizing deep learning architectures, David Baker 's team [11] used AI technology to design a serine hydrolase from scratch, which has a catalytic efficiency 60000 times higher than similar enzymes previously designed. Jiangnan University researchers [12] devised the machine learning-based iCASE framework, enabling simultaneous thermal stability and activity improvements in industrial enzymes through multi-PKa state simulations and conformational mobility analysis. These AI methodologies establish new paradigms for rational enzyme optimization critical in biomanufacturing applications. In addition, AI technology is also used to guide the evolution and optimization of enzymes.

In addition, Baassi et al. [13] designed a QSAR model to predict the biological activity of compounds, combined with molecular docking to study the binding mode of drugs and targets, and verified its stability and interaction mechanism by molecular dynamics simulation. This method provides a new strategy and theoretical support

for the drug design of HIV-1 protease inhibitors.

In Liu et al.'s study [14], a new method based on the large language model GPT-4 (GPT4Kinase) was proposed for high-precision prediction of the binding affinity between kinases and inhibitors. The prediction accuracy of GPT4Kinase on the RAF kinase dataset reached 87.31%, and the accuracy on the overall dataset was 77.00%. The literature also compared GPT4Kinase with other representative prediction methods and found that it was significantly better than other methods, such as AutoDock Vina (21.21%), BatchDTA (52%), and KIPP (59.60%). Through this interdisciplinary approach, inhibitors with high affinity for target kinases can be identified, which can promote the development of new small molecule drugs after subsequent validation. In a study published in 2025, Landwehr et al. [15] developed a machine learning (ML) guided cell-free expression platform to accelerate enzyme engineering, addressing the limitations of traditional enzyme engineering methods such as low throughput screening and difficulty in rapidly generating large amounts of sequence function relationship datasets, resulting in slow enzyme optimization processes.

This computational paradigm establishes innovative pathways for enhancing enzymatic adaptability while redefining industrial biocatalyst optimization. Contemporary AI applications in enzyme engineering extend beyond de novo design and evolutionary strategies to encompass precise activity prediction, notably demonstrated through machine learning models that accurately forecast catalytic parameters validated via high-throughput experimentation. Such synergistic integration of predictive and synthetic approaches enables the creation of artificial enzymes rivaling natural counterparts in functionality. Collectively, AI-driven advances – spanning predictive analytics, structural prototyping, and adaptive refinement – constitute a transformative framework for next-generation biocatalyst development.

4.3 Multi omics data integration

Artificial intelligence (AI) is also widely used in multi-omics data integration. The accelerated development of multi-omics methodologies has positioned AI as an indispensable tool for synthesizing diverse omics data (genomic, transcriptomic, proteomic, metabolic), fundamentally reshaping our comprehension of complex biosystems. A review published in 2025 [16] outlined an AI-powered multi-tier computational architecture that connects biological hierarchies through machine learning-driven mechanism integration, enabling predictive insights into genotype-environment-phenotype interdependencies with configuration-independent validation. This paradigm further demonstrates non-trivial potential for revolutionizing therapeutic target identification, biomarker mining, and stratified pharmacotherapeutic innovation.

In 2019, Sartor et al. [17] proposed a machine learning-based method to improve the annotation of plant genomes by using genome-wide epigenetic markers (such as DNA methylation and histone modification). By analyzing the reference genome of maize inbred line B73, more than 60,000 protein-coding genes were annotated, of which about two-thirds were transcribed and designated as filtered gene set (FGS). The results of this study show that this method can accurately classify the gene sets transcribed in different inbred lines and highlight the potential of using chromatin information to improve functional gene annotation. Bai et al. [18] utilized machine learning, particularly the AutoGluon Tabular framework, combined with multi omics data from Arabidopsis thaliana to predict genes involved in the biosynthesis of plant specific metabolites (PSM), with a focus on the three major categories of PSM: terpenes, alkaloids, and phenols. Research has found that genomic and proteomic features are key factors in model performance. The new model constructed using only these key features performs better in Arabidopsis than models containing transcriptome and epigenome features. The model has been validated in corn and tomato, and external validation in grapes and poppies shows its broad potential for application, especially when there is more species data, it can significantly improve the accuracy of PSM synthase gene prediction. In 2024, Huawei and King Abdullah University of Science and Technology (KAUST) jointly developed the AutoBA system [19], which pioneered the application of AI to fully automated analysis of multi-omics data. The AutoBA system is dedicated to simplifying the tedious data analysis process. By integrating multi-omics data, it provides an efficient and automated solution to accelerate the research and production of plant secondary metabolites.

These investigations reveal AI's unparalleled capacity for synthesizing multi-omics datasets. The synergy between multi-omics platforms and AI architectures inversely neglects neither their catalytic role in amplifying high-value compound biosynthesis nor their facilitation of breakthrough-centric biomedical inquiries, ultimately enabling novel methodological paradigms for biotechnology advancement.

5 Conclusion

AI-innovated metabolic optimization holds unavoidable relevance for bioactive compound biosynthesis in ethnopharmacology. As transformative bioinformatics instrumentation, this computational paradigm critically reconfigures biotechnological workflows through machine learning-mediated big-data analytics, enabling rapid cannabinoid-like screening and hierarchical validation of traditional phytochemical candidates. It can optimize microbial metabolic pathways and improve the biosynthesis efficiency of active ingredients in traditional Chinese medicine.

The application of AI technology in the research of traditional Chinese medicine has greatly improved the efficiency of research and development of traditional Chinese medicine. Through AI-assisted design, such as network pharmacology technology, traditional Chinese medicine components with good pharmacological effects have been developed, which makes traditional Chinese

medicine more easily accepted by the international medical community and can greatly promote the international influence of traditional Chinese medicine.

This review critically examines AI implementation paradigms in contemporary metabolic engineering, focusing on selected cases with pharmacological implications. While model organisms (e.g., *Saccharomyces cerevisiae*, *E. coli*, Solanaceae species) have enabled exogenous pathway engineering for select high-value compounds, substantial natural/non-natural bioactive products with therapeutic potential remain non-trivial in biosynthetic elucidation. Current non-native pathway design primarily relies on enzyme promiscuity exploitation coupled with directed evolution frameworks, rather than predictive bio-design approaches. The development of transformative AI-guided metabolic networks, particularly for non-canonical reaction catalysis, holds imminent potential to address existing pathway modularization challenges. Future biomanufacturing applications will likely demonstrate unprecedented scalability in producing structurally diverse therapeutic agents through iterative in silico-augmented pathway refinement, ultimately advancing pharmacotherapeutic optimization.

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