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From cryptic gene clusters to bioactive metabolites: the role of AI in advancing fungal endophytes research

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Abstract: This study reports on the current state of the application of AI in the study of Fungal Endophytes. It highlights how AI-powered processes help in the genome mining and BGC annotation; how they are used in predicting metabolite structure and biological activity; how AI-driven culture models can optimize fungal fermentation and expression; and how, in combination with multi-omics measurements, AI is a powerful instrument to unlock the metabolic potential of fungal endophytes. Finally, further fields of application of AI models in understanding secondary metabolisms and researching anticancer drugs are reported. A flowchart and multiple panels help illustrate and represent the topics treated.

INTRODUCTION

Plant endophytic microbiomes, particularly fungal endophytes, are increasingly recognized as a prolific, yet underexplored, source of bioactive secondary metabolites (SMs) with significant pharmaceutical potential (Rajagopal *et al.* 2012). Endophytic fungi isolated from hydrophytes demonstrated rich mycodiversity and significant biotechnological potential (Rajagopal *et al.* 2012). Particularly fungal endophytes of these microbial communities have demonstrated the capacity to produce compounds with anticancer, antiviral, and antibacterial activity, including well-known molecules like paclitaxel and cryptocyanin (Hashem *et al.* 2023; Adeleke & Babalola 2021). Antibiofilm activity and molecular docking studies of bioactive secondary metabolites have been carried from *Aspergillus nidulans* on oral *Candida albicans* (Meenambiga & Rajagopal 2018). Endophytic fungi derived from marine algae are also being studied (Kalyanaraman *et al.* 2025). The co-evolution of endophytes with their host plants has resulted in unique biosynthetic gene clusters (BGCs) that rival or exceed those found in free-living microbes (Pillay *et al.* 2022; Ali *et al.* 2024). However, many of these BGCs remain silent under standard laboratory conditions and this silence presents a major challenge for drug discovery in endophytes (Reen *et al.* 2015; Tomm, Ucciferri & Ross 2019). Recent emergence of multi-omics technology, including transcriptomics, metabolomics, regulomes, and genomics, has now provided the opportunity to rationally determine and map these dark biosynthesis-related pathways (Sagita *et al.* 2021; Bhardwaj *et al.* 2023; Chen *et al.* 2023; Hannigan *et al.* 2019; Riedling, Walker & Rokas 2024). In addition to making predictions on the best conditions to use in cultures or environmental stimuli to induce dormant groups of genes and understanding complex regulatory interactions, AI models can also be used to predict the most favourable conditions in supporting the growth of organisms as in BGC mining (Verma *et al.* 2023; Chowdhary, Arora & Sharma 2022, Shu *et al.* 2024). Simulating ecological dynamics of interactions among microbes and plants is also becoming popular in AI, with biocontrol to sustainable agriculture being some of the applications. It is a paradigm shift in the discovery of natural products through endophytes motivated by integration methods that involve natural intelligence, synthetic biology, systems biology, and bioinformatics (Gakuubi *et al.* 2021). This accruing progress of using plant endophytes as a new approach to natural drug discovery makes this

approach exceptionally promising. To fully deliver on this promise, it will be necessary to explore and exploit microbial metabolic dark matter in an organized manner with the help of a mix of genomics, AI, and functional validation methods (Sagita *et al.* 2021).

AI-POWERED GENOME MINING AND BGC ANNOTATION

One important recent development in artificial intelligence (AI) is deep learning (DL) as it has transformed genome mining in fungal endophytes by allowing more specific detection and annotation of biosynthetic gene clusters (BGCs). Widely applicable tools like DeepBGC that rely on convolutional neural networks (CNNs) trained on datasets of BGCs can allow more precise identification of the borders between BGCs even in complex fungal genomes where traditional metabolic markers are usually missing or altered (Hannigan *et al.* 2019; Roy *et al.* 2025; Zhou *et al.* 2025; Mansourvar *et al.* 2025) (Fig. 1 & 2, Table 1). Effector-GAN can predict fungal effector proteins using the generative adversarial networks and pretrained deep representation learning methods, particularly of fungal endophytes that often contain cryptic or unique clusters of genes due to the evolutionary changes in adaptation to various ecological niches and co-evolution with host plants (Gakuubi *et al.* 2021; Wang *et al.* 2022; Chen *et al.* 2023) (Fig. 1 & 2, Table 1). Endophyte research commonly uses draft genomes or metagenomic datasets due to microbial complexity and sequencing difficulties; these models enhance the detection of fragmented or novel BGCs (Theobald *et al.* 2018; Wang *et al.* 2025). In contrast to traditional metabolic markers that are often missing or altered, these AI-driven approaches provide a more robust framework for identifying BGCs. While conventional methods struggle with the complexity of draft genomes and fragmented datasets, AI models offer higher sensitivity and precision, enabling the discovery of cryptic biosynthetic gene clusters that were previously undetectable. AI-powered models help identify promoter elements, transcription factor binding sites, and epigenetic markers that control low-expression or silence clusters (Gupta *et al.* 2020; Liu *et al.* 2025). With the use of scoring systems based on structural novelty, predicted pharmacological potential, and biosynthetic feasibility, network-based prioritization frameworks have advanced beyond simple detection to incorporate outputs from genome mining tools such as antiSMASH, MIBiG, and PRISM (Ming *et al.* 2023; Yuan *et al.* 2023; Liu *et al.* 2022; Zakariyah *et al.* 2024; Kumari *et al.* 2025) (Fig. 1 & 2, Table 1). Bayesian inference models and graph neural networks (GNNs) are being utilized more and more to simulate metabolite pathway interactions and infer gene co-expression patterns, and endophytic fungal ITS data phylogenetic analysis are being obtained utilizing massive parallel Bayesian tree inference with exabytes (Montero-Vargas, Umaña-Jiménez, Escudero-Leiva & Chaverri-Echandi 2020; Pöttker *et al.* 2023) (Fig. 1 & 2, Table 1). This provides functional context and prioritizes BGCs that are most likely to produce bioactive compounds (Al Shami & Mousa 2026). The identification of desired clusters for subsequent uses, such as chemical profiling, synthetic biology, or heterologous expression, is further improved by combining AI algorithms with multi-omics data (e.g. transcriptomics, epigenomics, and metabolomics) (Shankar & Sharma 2022). The practical utility of AI and multi-omics integration is exemplified by the discovery of previously hidden novel bioactive metabolites. For instance, genome mining and in silico approaches enabled the identification of Asperterpenoids A and B from the endophytic fungus *Aspergillus terreus*, which exhibit potent BACE1 inhibitory activity (Qi *et al.* 2016). Similarly, recent deep-mining strategies have linked cryptic biosynthetic gene clusters to novel chemical scaffolds across fungal taxa, highlighting the potential of AI to shift natural product discovery toward a more predictive and targeted paradigm (Shishodia *et al.* 2025) (Fig. 1 & 2, Table 1).

PREDICTING METABOLITE STRUCTURE AND BIOLOGICAL ACTIVITY IN FUNGAL ENDOPHYTES

Models based on artificial intelligence that identify epigenetic marks, transcription factor binding sites, and promoter elements which regulate clusters of genes that are quiescent or lowly expressed are also offered (Riedling, Walker & Rokas 2024; Wang & Mao 2025). Genome mining and screening show the presence of a secondary metabolite production in the endophytic fungus *Dactylonectria alcacerensis* CT-6 (Ming *et al.* 2023). Network-based prioritization systems have advanced past just detection using genome-mining tools, e.g. antiSMASH, MIBiG, and PRISM (Ming *et al.* 2023; Wang *et al.* 2025; Liu *et al.* 2021) (Fig. 1 & 2, Table 1). Unlike traditional rule-based methods that often overlook silent clusters, these AI-driven platforms offer significantly higher sensitivity by recognizing deep patterns in fragmented metagenomic data. Besides simple detection,

these models are now capable of predicting core chemical scaffolds and estimating biological activities through automated docking and scoring functions. They do this using scoring methods that consider biosynthetic feasibility, expected pharmacological potential, and structural originality (Kumari *et al.* 2025). These AI-generated molecular structures are subjected to in silico docking simulations against a range of biological targets, such as kinases, viral proteases, and oncogenic receptors, enabling high-throughput virtual screening procedures (Munshi *et al.* 2022). Docking research supports the idea that soybean-associated endophytic fungus could be a source of anti-COVID-19 metabolites (El-Hawary *et al.* 2021). Bayesian inference models and graph neural networks (GNNs) are increasingly being used to describe gene co-expression patterns and metabolite pathway interactions (Pöttker *et al.* 2023) (Fig. 1 & 2, Table 1). This ranks BGCs according to their likelihood of producing bioactive compounds and gives functional context. Further enhancements are the selection of possible clusters for use in chemical profiling, synthetic biology, heterologous expression, and other downstream applications (Hyde *et al.* 2024; Prakash *et al.* 2025; Shankar & Sharma 2022). These prediction filters aid in focusing downstream efforts on the most promising candidates by early exclusion of substances with significant cytotoxicity or poor pharmacokinetic characteristics (Wen *et al.* 2022). AI-driven methods would speed up drug discovery from endophytes by bridging the gap between expected biosynthetic capacity and empirically proven secondary metabolite production, as endophytic fungi are underrepresented in genomic databases (Kalita *et al.* 2025). This lack of comprehensive genomic data creates a significant 'knowledge gap', making it difficult for AI models to accurately distinguish between rare endophytic BGCs and common soil-dwelling fungal clusters. Furthermore, without a diverse reference library, many unique metabolic pathways remain 'dark' or unannotated, limiting the potential for discovering truly novel bioactive compounds. Addressing this gap through large-scale sequencing of diverse endophytic taxa is essential to improve the predictive accuracy of future AI-driven discovery pipelines.

AI IN ENDOPHYTIC FUNGAL FERMENTATION AND EXPRESSION OPTIMIZATION

Under typical laboratory conditions, many fungal endophyte biosynthetic gene clusters (BGCs) do not exhibit transcriptional activity (Yang *et al.* 2019). AI-driven culture models increase metabolite expression by optimizing growth parameters, providing potent treatments (Garg *et al.* 2025). The most efficient mixtures of carbon sources, micronutrients, pH, temperature, and co-culture combinations, such as the presence of host plant tissues or other microorganisms, are determined using the methods of multi-objective evolutionary algorithms and Bayesian optimization, which subsequently leads to the activation of biosynthetic gene clusters (Bode 2002; Li *et al.* 2021) (Fig. 1 & 2, Table 1). AI-based algorithms efficiently handle such complex variable interactions, unlike traditional one-factor-at-a-time (He *et al.* 2019; Liu *et al.* 2025). Lab-on-a-chip systems that generate real-time sensor data are connected to more advanced bioprocessing systems to provide reinforcement learning models, which subsequently dynamically regulate fermentation parameters (Aghdam & Brown 2021; Megnidio-Tchoukouegno, Gueguim Kana & Bancolé 2022). Based on the existing information, including genomic data of the host plant, fungal metabolic profiles, and known signalling molecules involved in plant-microbe interactions, predictive machine-learning models can detect the endophytic colonization of rice cultivar tissues with isolates of *Beauveria bassiana* and evaluate their possibility to be used as bio-controlling agents against the rice stem borer (Megnidio-Tchoukouegno, Gueguim Kana & Bancolé 2022). It has been established that fungal endophytes with the ability to express silent biosynthetic gene clusters can be predictably induced and that the production of metabolites can be greatly enhanced by adaptive control methods that adjust cultivation conditions to metabolic production (Pillay *et al.* 2022). Lastly, while co-expression analysis is a fundamental statistical approach, when integrated with AI-driven regulatory network modelling, it reveals deeper insights into fungal pathogenicity. For instance, studies show that the PacC transcription factor could be a factor in the pathogenicity of the Chinese hickory in the presence of the transcription factor, which is known as *Botryosphaeria dothidea* (Liang *et al.* 2025) (Fig. 1 & 2, Table 1).

COMBINING AI AND MULTI-OMICS TO ACTIVATE FUNGAL ENDOPHYTE PATHWAYS

Integrating multi-omics measurements with AI modelling is also necessary to unlock the entire metabolic potential of fungal endophytes (Shishodia *et al.* 2025; Liu *et al.* 2025) (Fig. 1 & 2, Table 1). By predicting which

BGCs are epigenetically repressed, models trained on epigenetic data such as histone modification maps, DNA methylation profiles, and RNA-seq expression levels can direct focused activation (Moore, Le & Fan 2013; Al Aboud, Tupper & Jialal 2023; Chen *et al.* 2023; Varghese, Rajeshkumar & Jisha 2025) (Fig. 1 & 2, Table 1). For instance, regulatory elements governing BGC expression can be found using AI-assisted analysis of Chip-seq, ATAC-seq, and RNA-seq data (Carrión *et al.* 2019; Motalebnejad *et al.* 2025). These AI-driven discoveries of BGC regulatory elements directly inform the precision design of CRISPR-based gene activation systems (CRISPRi). By utilizing guide RNAs targeted to the AI-identified epigenetic 'hotspots' (Aghdam & Brown 2021; Chowdhary, Arora & Sharma 2022; Zhao *et al.* 2024), researchers can precisely modify metabolic pathways to induce the expression of silent gene clusters. This targeted activation provides the high-quality, validated experimental data required to feed back into deep multimodal AI frameworks, which integrate transcriptomic, proteomic, and metabolomic data to show how external signals, such as cues derived from the plant host and internal cellular networks, interact to control secondary metabolism in endophytes (Yuan *et al.* 2019; Chen *et al.* 2022). To create logical plans to control metabolite production in plants and in vitro, these integrative methods are essential as they transition fungal biotechnology from traditional trial-and-error discovery to a predictive, design-driven science. By bridging the gap between computational BGC prioritization and experimental validation through CRISPRi, these frameworks enable the sustainable large-scale production of high-value fungal metabolites, ultimately accelerating the drug discovery pipeline for novel antimicrobials and anticancer agents (Jha *et al.* 2023).

AI MEETS ECOSYSTEMS IN FUNGAL ENDOPHYTE DISCOVERY

Fungal regulatory genetics and environmental modelling are combined in the new field of coelomic to clarify how natural stresses affect secondary metabolism (Tiwari, Adil & Park 2025; Tiwari & Bae 2022). AI models, especially deep neural networks and ensemble techniques like decision trees, anticipate environmentally inducible BGCs in fungal endophytes by simulating abiotic challenges, including salinity, drought, and temperature fluctuations. (Zhang *et al.* 2024). The predictions thus allow for the formulation of in situ mimetic studies that replicate ecological triggers in laboratories (Kaur *et al.* 2024). These approaches provide essential knowledge and highlight new opportunities and challenges in natural product drug discovery from endophytic fungi (Tiwari, Adil & Park 2022) (Fig. 1 & 2, Table 1).

COMPELLING CASE EXAMPLES IN AI-DRIVEN ENDOPHYTE APPLICATIONS

AI is already demonstrating substantial practical value across fungal endophyte research pipelines (Kunwar *et al.* 2023). In anticancer drug discovery, deep learning platforms have screened thousands of predicted fungal metabolites against breast cancer receptor targets, efficiently prioritizing candidates based on predicted bioactivity, selectivity, and toxicity profiles (Varghese *et al.* 2024). In agriculture, Random Forest and Gradient Boosting machine learning models identified *Beauveria bassiana* strains with enhanced colonization ability in rice under heat stress (Megnidio-Tchoukouegno, Gueguim Kana & Bancole 2022). Importantly, AI tools are addressing challenges posed by unculturable fungi by mining early metagenomic sequences to predict cryptic BGCs. These predictions are primarily based on conserved biosynthetic motifs and structural patterns recognized by deep learning models from established BGC databases. Since these mushrooms are non-cultivable, the 'ground truth' for evaluation is established through synthetic biology, where AI-predicted gene clusters are synthesized and expressed in well-characterized heterologous hosts. This functional expression serves as the critical reference point to validate whether the predicted BGCs are indeed capable of producing the expected chemical diversity (Figueiredo *et al.* 2025) (Fig. 1 & 2, Table 1).

ETHICAL, REGULATORY, AND PRACTICAL FRAMEWORK FOR AI-GUIDED FUNGAL ENDOPHYTES RESEARCH

As AI accelerates fungal endophyte bioprospecting, strict adherence to ethical and regulatory frameworks is essential (Gupta & Kumar, 2024). Compliance with the Nagoya Protocol and Access and Benefit-Sharing (ABS) agreements ensures the equitable use of microbial genetic resources, particularly those derived from biodiversity-rich or indigenous territories (Sharma *et al.* 2018). Embracing FAIR data principles (Findable, Accessible, Interoperable, and Reusable) fosters transparency, reproducibility, and collaborative progress in AI-assisted discovery (González-Rodríguez *et al.* 2024). Moreover, forming partnerships with local scientists,

indigenous communities, and conservation organizations ensures that AI-enabled research advances both scientific innovation and socio-environmental stewardship. Such coordination is paramount to ensuring equitable benefit-sharing, where pharmacological discoveries derived from traditional ecological knowledge are co-developed with local stakeholders. This inclusive approach not only strengthens the accuracy of AI models by integrating site-specific environmental data but also protects the sovereignty of biological resources, aligning bioprospecting with sustainable and ethical frameworks (Tella *et al.* 2025) (Table 1).

CONCLUSION

The integration of artificial intelligence (AI) with multi-omics technologies has ushered in a new era of drug discovery from fungal endophytes. By overcoming the challenge of silent BGCs through advanced genome mining, predictive modelling, and epigenetic manipulation, AI enables the systematic exploration of previously inaccessible metabolic diversity. Machine learning and deep learning tools enhance BGC annotation, metabolite structure prediction, and bioactivity profiling, while AI-driven fermentation optimization and multi-omics integration unlock novel pathways. Additionally, coelomic provides insights into environmental regulation of fungal metabolism, guiding targeted activation strategies. Real-world applications in drug discovery and agriculture highlight AI's transformative potential, though ethical and regulatory considerations must remain central to bioprospecting efforts. Moving forward, the synergy between AI, synthetic biology, and functional validation will be crucial in harnessing fungal endophytes as a sustainable source of next-generation therapeutics. This interdisciplinary approach not only accelerates natural product discovery but also ensures that scientific advancements align with ecological and ethical stewardship.

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DECLARATION OF CONFLICT OF INTEREST

Regarding the publication of this review, the authors affirm that they have no conflicts of interest.

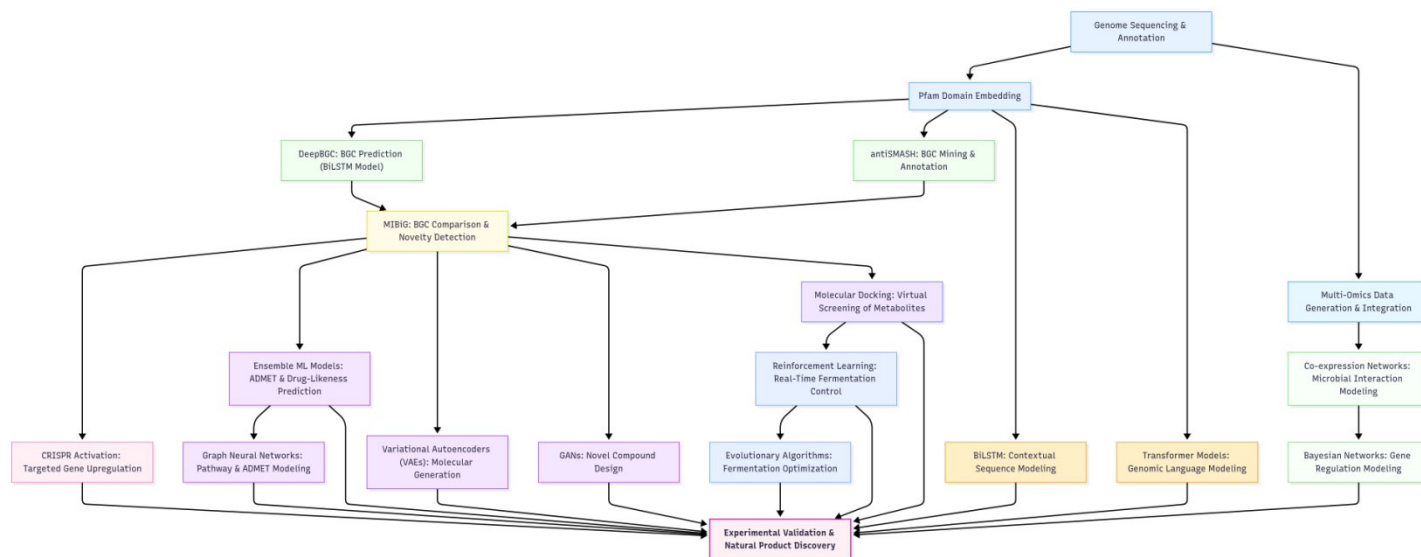


Figure 1 (above). The workflow for the study and the logical relationships between the several experimental or data processing procedures are depicted in this flowchart. Boxes stand for significant stages or analytical points, whereas arrows illustrate the development, interdependencies, and integration of results.

Figures 2i to 2vi (below). The figures represent multiple panels (AI-A6, BI-B7, and CI-C3), each representing distinct outcomes or experimental conditions in the study. Each panel's size is standardized to ensure consistent comparison. The arrangement allows for comprehensive visualization and facilitates the identification of key differences across the tested variables. Panel labels correspond to the different categories or treatments evaluated and are clearly marked for easy reference in the main text.

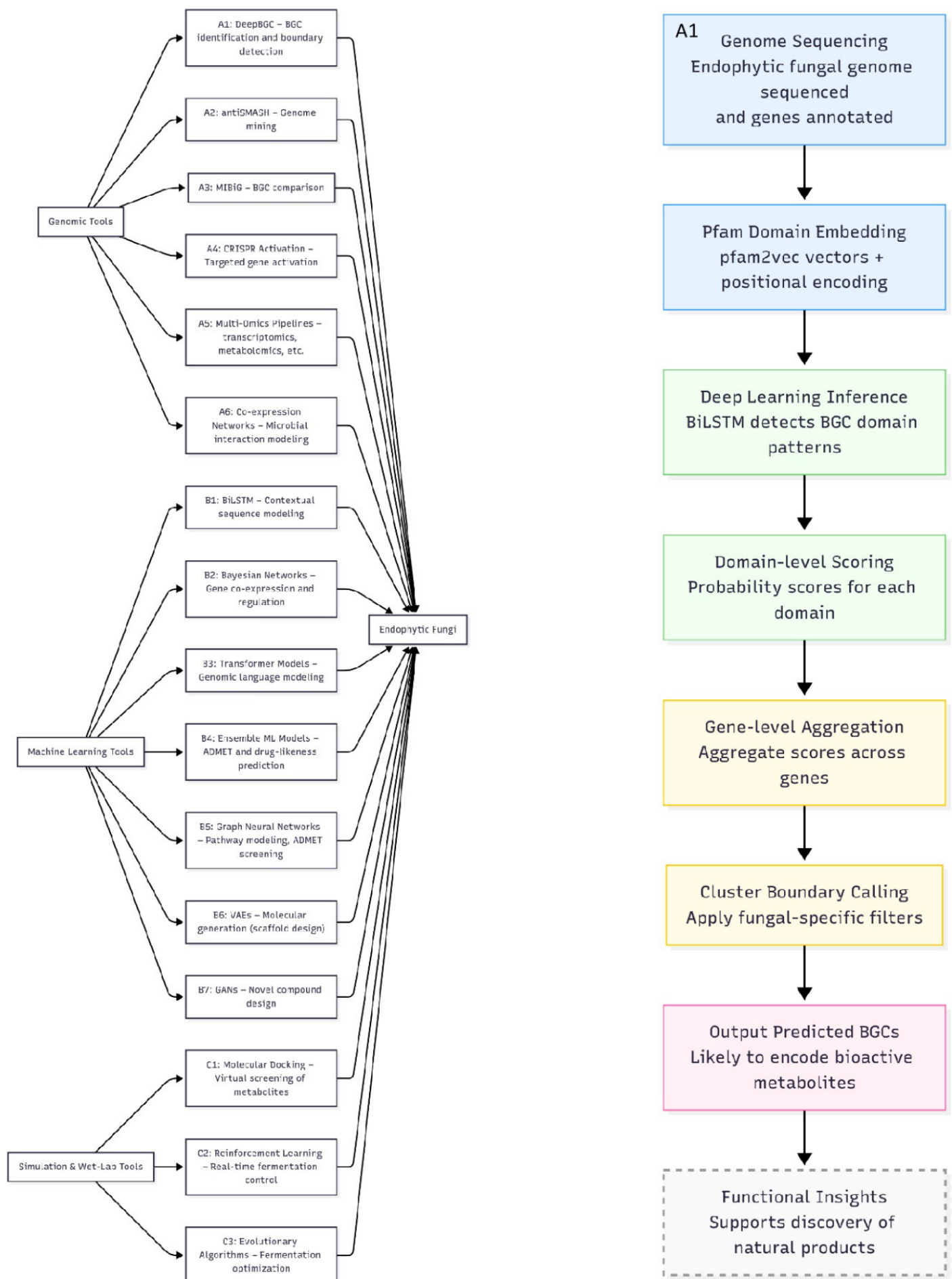


Fig. 2i

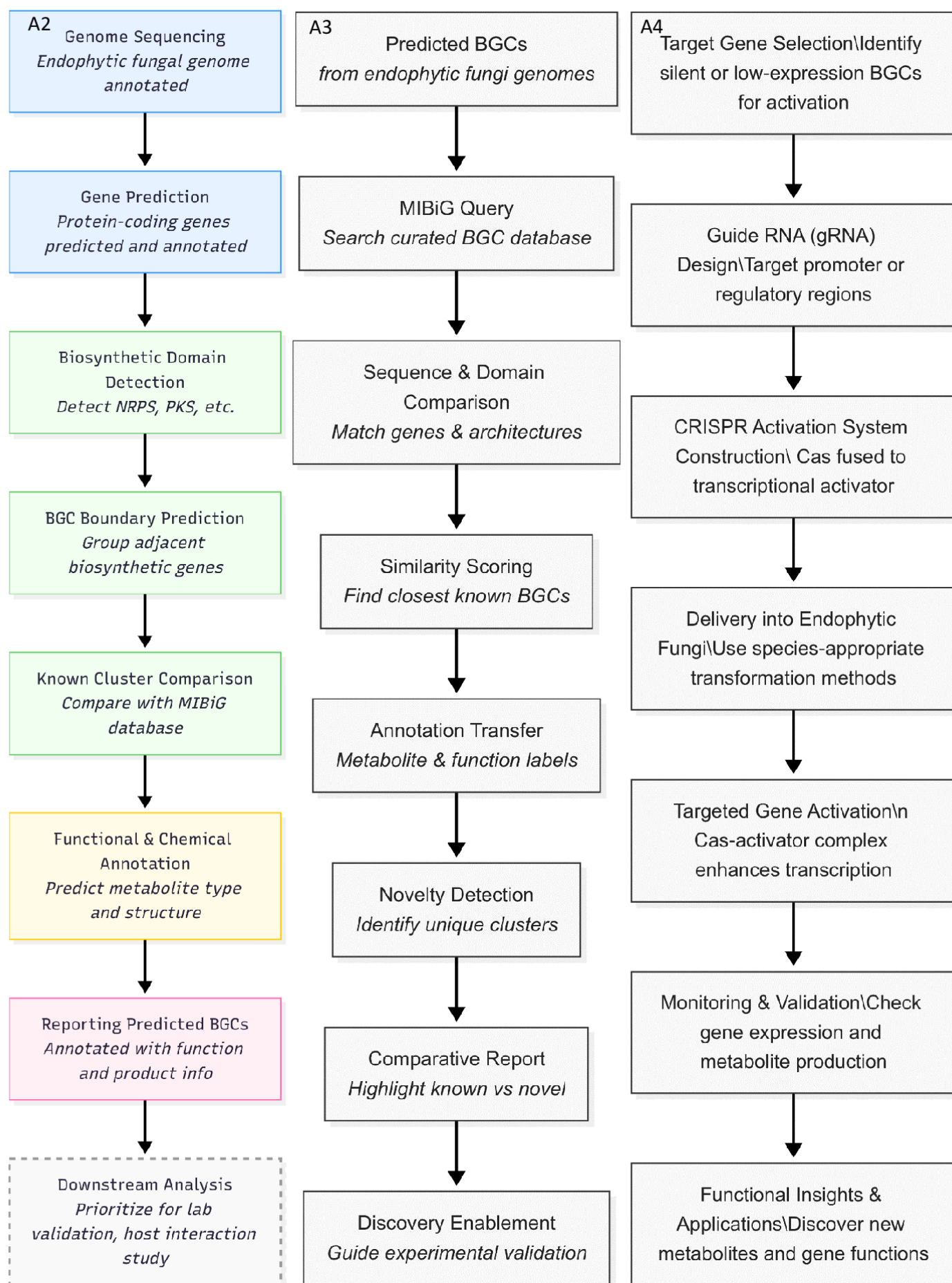


Fig. 2ii

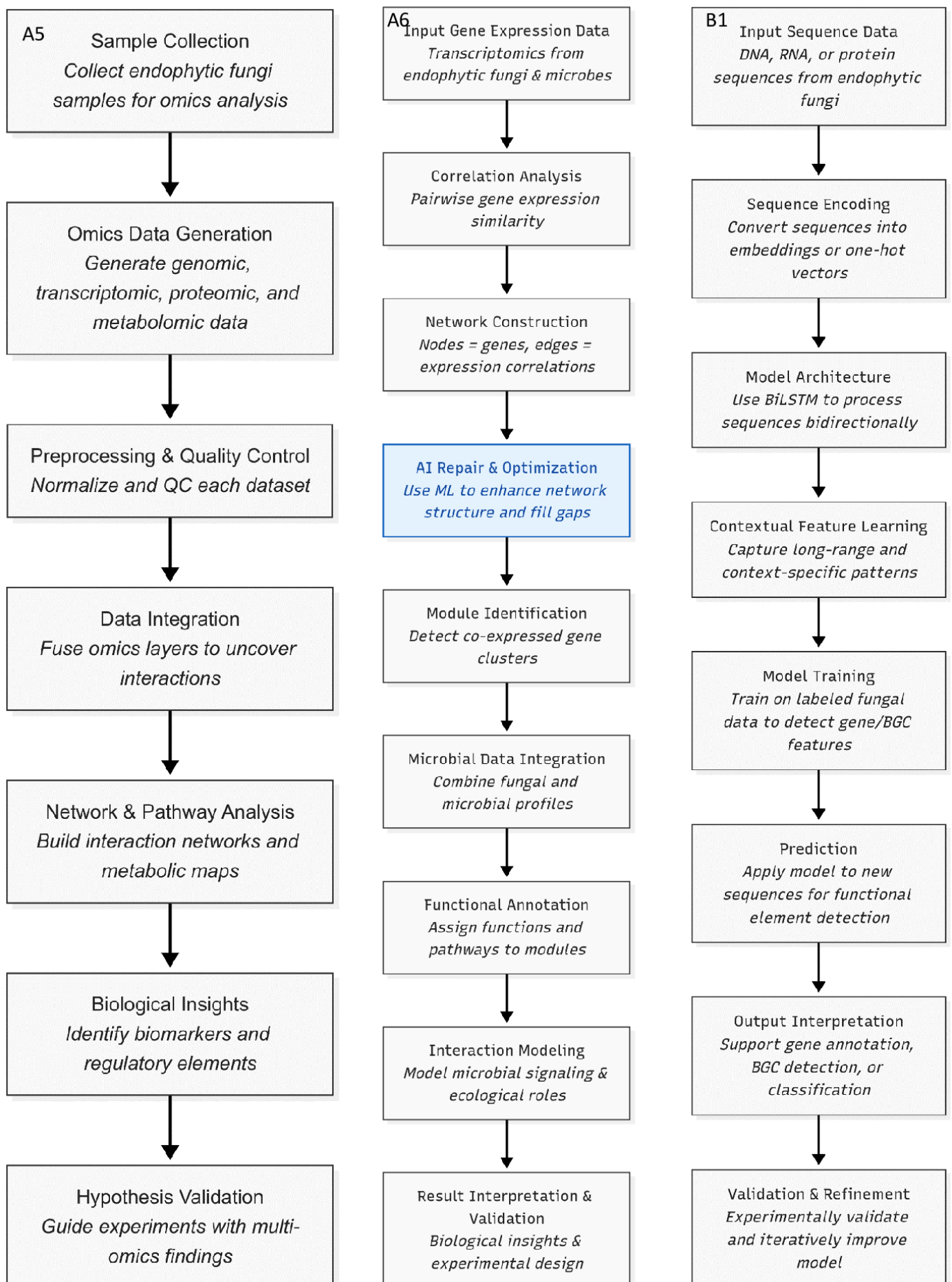


Fig. 2iii

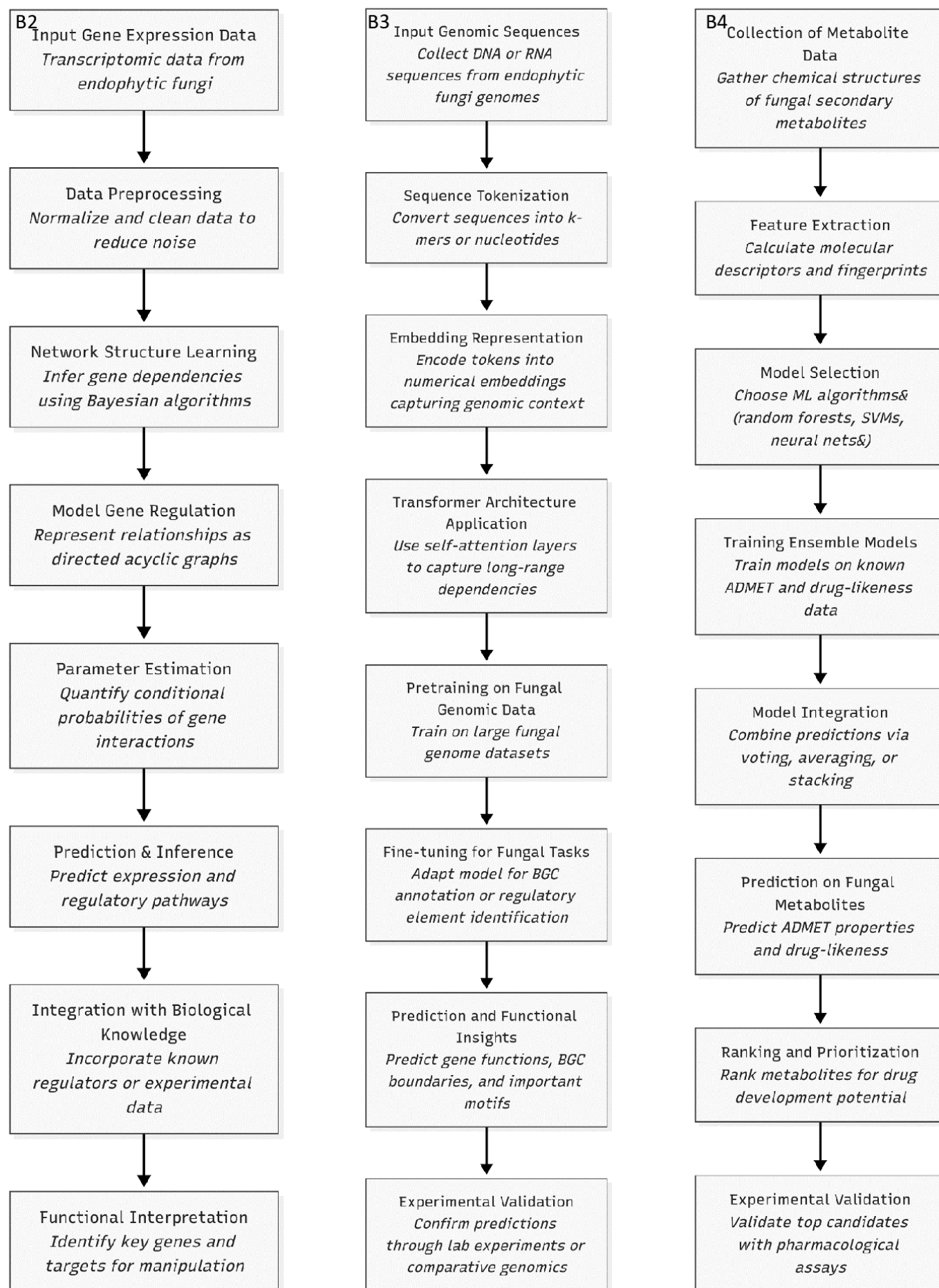


Fig. 2iv

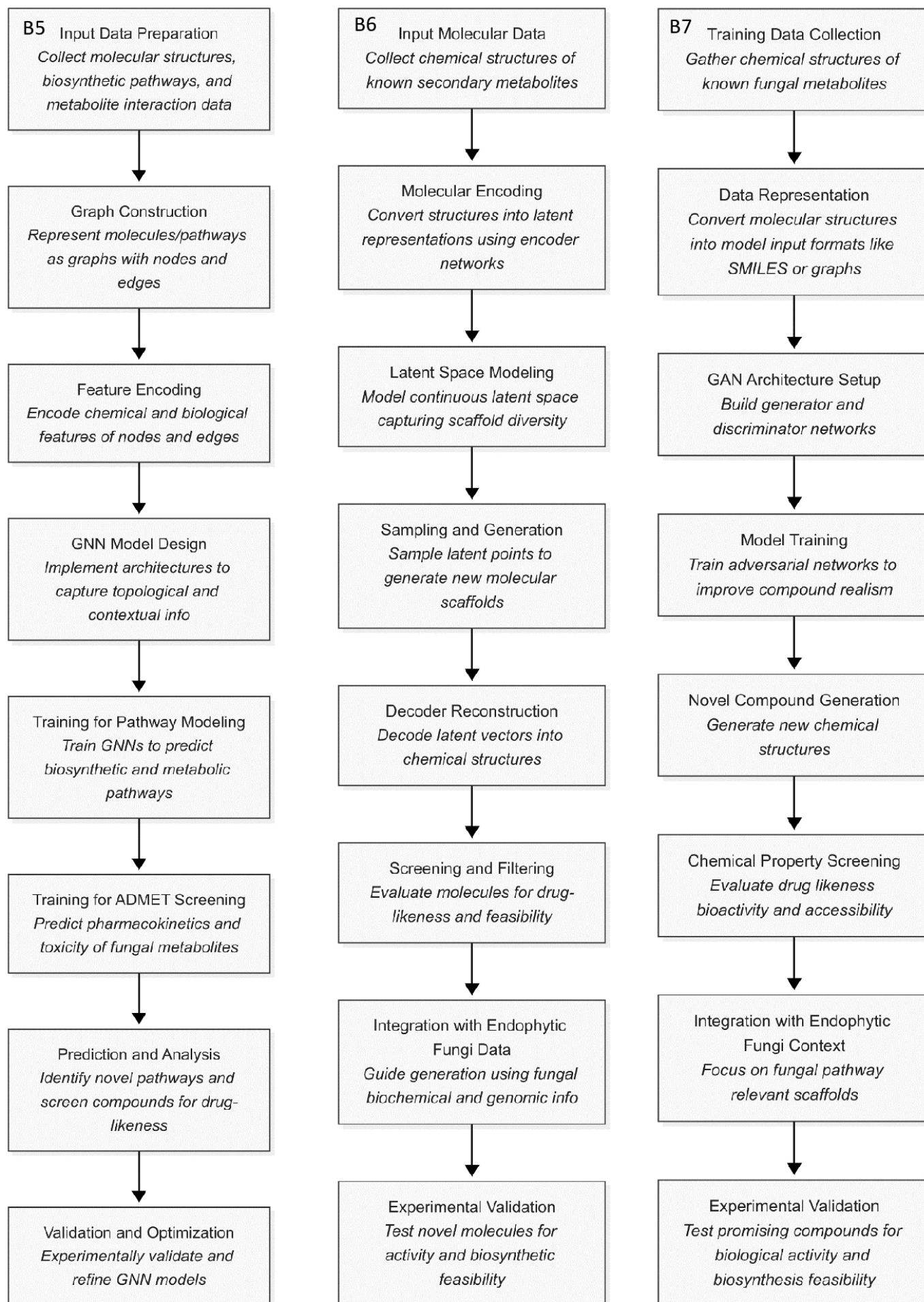


Fig. 2v

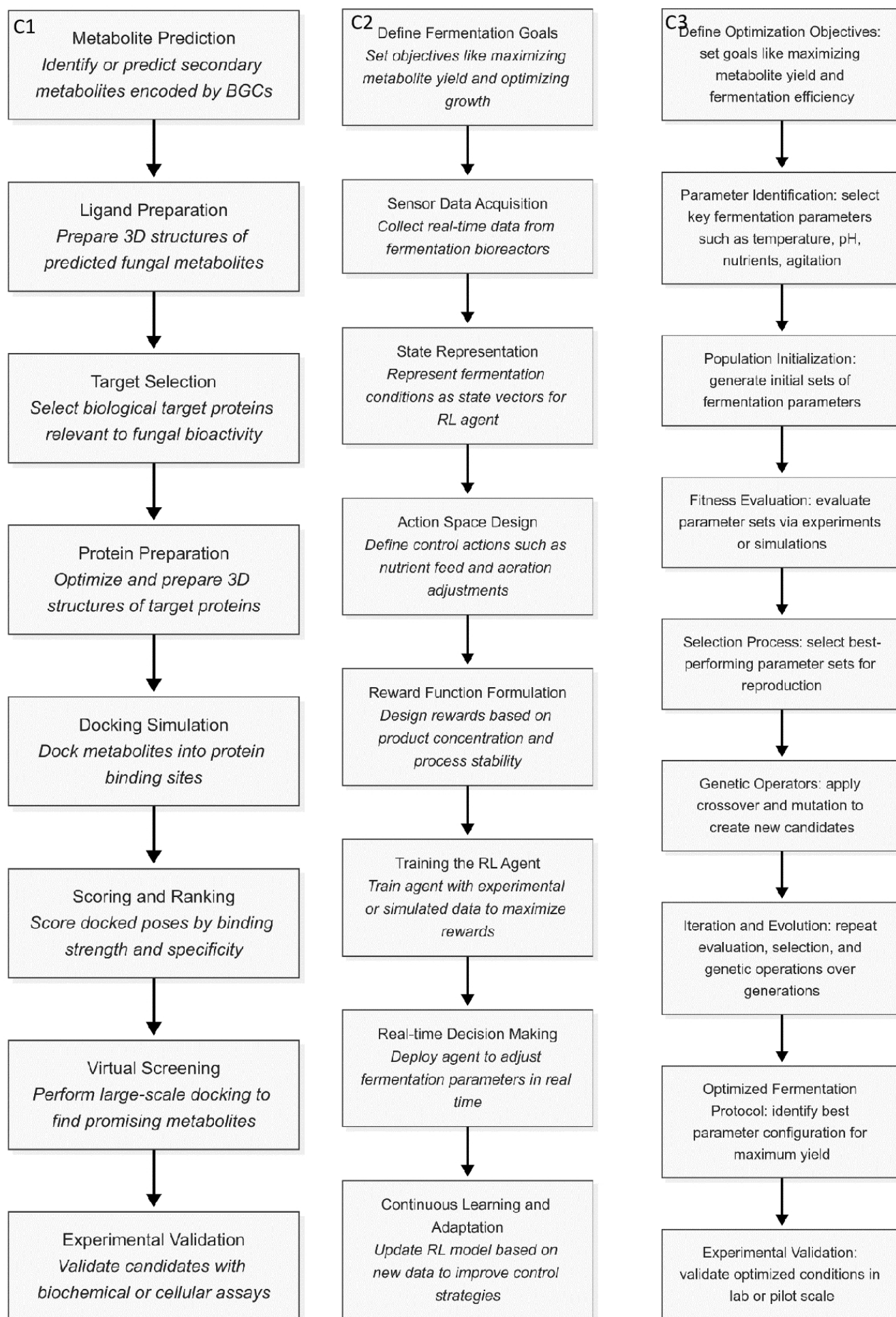


Fig. 2vi

Tool / Model	Application	Use Case / Output	References
DeepBGC (CNN-based)	BGC identification and boundary detection	Detects cryptic biosynthetic gene clusters in fungal genomes	Hannigan <i>et al.</i> 2019
antiSMASH	Genome mining	Annotates known and novel BGCs from genomic sequences	Liu <i>et al.</i> 2021
MIBiG	Reference database for BGC comparison	Matches BGCs with characterized clusters and known metabolites	Ming <i>et al.</i> 2023
BiLSTM (Bidirectional LSTM)	Contextual sequence modelling	Predicts long-range dependencies in regulatory DNA sequences	Tiwari & Bae 2022
Transformer Models (e.g., BERT)	Genomic language modelling	Identifies regulatory motifs and transcription factor binding sites	Yu <i>et al.</i> 2024
Graph Neural Networks (GNNs)	Pathway modelling, ADMET screening	Models gene-gene interactions, pharmacokinetics, and toxicology	Pöttker <i>et al.</i> 2023
Bayesian Networks	Gene co-expression and regulation	Predicts gene interactions under variable environmental conditions	Montero-Vargas <i>et al.</i> 2020
Variational Autoencoders (VAEs)	Molecular generation	Designs novel metabolite scaffolds based on learned chemical features	Roy <i>et al.</i> 2025
Generative Adversarial Networks (GANs)	Synthetic compound generation	Creates synthetic compound structures mimicking real metabolite scaffolds	Wang <i>et al.</i> 2022
Molecular Docking Algorithms	Virtual screening	Assesses binding affinity of predicted metabolites to disease-related proteins	El-Hawary <i>et al.</i> 2021
Ensemble ML Models	Drug-likeness prediction	Filters out cytotoxic or poorly absorbed drug candidates (ADMET profiling)	Chen <i>et al.</i> 2023
Evolutionary Algorithms	Fermentation optimization	Determines ideal culture conditions for optimal metabolite production	Li <i>et al.</i> 2021
Reinforcement Learning (RL)	Real-time bioprocess control	Adjusts fermentation parameters (pH, temperature) based on sensor feedback	Megnidio-Tchoukouegno <i>et al.</i> 2022
CRISPR Activation Systems	Targeted gene activation	Enables precise BGC regulation via gRNA-guided transcriptional tuning	Chowdhary <i>et al.</i> 2022; Zhao <i>et al.</i> 2024
Multi-Omics Integration Pipelines	Data fusion (transcriptomics, metabolomics, etc.)	Models comprehensive regulation of metabolic pathways	Shankar & Sharma 2022
Co-expression Network Analysis	Microbial interaction modelling	Predicts inter-kingdom signalling (e.g., quorum sensing) affecting BGC dynamics	Liang <i>et al.</i> 2025

Table 1. Artificial Intelligence Tools and Techniques in Fungal Endophytes Research

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