Frontiers in Life Sciences Research
Vol. 1, No. 3, Jul - Sep 2025, pp. 8-13
ISSN: 3107-5274, DOI: https://doi.org/10.17051/FLSR/01.03.02

Environmental DNA and AI-Driven Drug Discovery: Unlocking Nature's Genomic Reservoirs for Novel Therapeutics

Shaik Sadulla[1], K P Uvarajan[2]

[1]Department of Electronics and Communication Engineering, KKR & KSR Institute of Technology and Sciences, Vinjanampadu, Guntur-522017, Andhra Pradesh, India, Email: sadulla09@gmail.com
[2]Department of Electronics and Communication Engineering, KSR College of Engineering, Tiruchengode Email: Uvarajan@ksrce.ac.in

Article Info

Article history:

Received : 07.07.2025
Revised : 13.08.2025
Accepted : 17.09.2025

Keywords:

Environmental DNA (eDNA),
artificial intelligence (AI),
metagenomics,
biosynthetic gene clusters (BGCs),
natural product discovery,
machine learning,
deep learning,
drug discovery,
antibiotics,
anticancer agents,
antiviral compounds.

ABSTRACT

The combination of the environmental DNA (eDNA) technology and the artificial intelligence (AI) offers a radical direction to quickening the discovery of natural products used in drugs. The low culturing efficiency, sampling bias, and limited access to genomic data, nearly all constrain conventional bioprospecting approaches, causing the underrepresentation of microbial diversity. eDNA overcomes such barriers by allowing direct genetic harvesting of diverse ecosystems, making unculturing microbial genomes accessible. Parallel AI-based bioinformatics, machine learning, and predictive modeling can provide potent analysis tools to analyze and understand intricate metagenomic data, reveal biosynthetic gene clusters (BGCs) and predict the structures and functions of encoded metabolites. This paper is an overview of the last developments in eDNA-based metagenomics and AI-based compound discovery pipelines. It suggests a methodological framework, which combines eDNA sampling, next-generation sequencing, AI-assisted BGC annotation, predictive metabolites, and virtual screening. Case studies demonstrate how effective such approach has been in revealing new antibiotic candidates that are active in diverse applications in multidrug-resistant bacteria, polyketide-derived anticancer leads, and antiviral secondary metabolites. Data indicate that discovery times are greatly shortened, the ratio of hits to leads is increased, and predictive accuracy is greater than in conventional methods. The results demonstrate the possible change in the eDNA-AI combination that will transform the world of drug discovery and the need to pursue sustainable bio-prospecting methods and biodiversity exploitation. Future studies must include explainable AI models, development of world repositories of eDNA, and the implementation of fair systems on how to share genomic resources.

1. INTRODUCTION

The identification of new therapeutics has become an order of focus in the contemporary research in biomedical studies. Traditional drug discovery pipelines have traditionally relied on the growth of microorganisms followed by extraction of natural products. It is, however, estimated that only less than 1 percent of microbial species are capable of being cultured in the laboratory leaving an enormous majority of the genomic and metabolic diversity unexplorable [1]. The bias is a major limitation in the discovery of new alcohols and anticancer, antiviral drugs, which is needed currently when drug resistance and emerging diseases are increasing healthcare burdens across the world. Environmental DNA (eDNA) has risen to fill this shortcoming as a revolutionary instrument. eDNA also makes available hitherto unreachable genomic data by allowing scientists to directly extract genetic material in soil, marine sediments, and extreme ecological niches without necessarily requiring cultivation to do so 【2】. Such a strategy has already proved capable of uncovering new biosynthetic gene clusters (BGCs), which encode therapeutically-relevant secondary metabolites. In parallel with these developments, the artificial intelligence (AI) has also been a potent facilitator of the drug discovery process. It is now possible to annotate metagenomic datasets quickly, predict chemical structures, and in silico screen a compound library using deep learning, graph neural networks, and transformer-based

models [3]. Nevertheless, even with its advancement, the recent studies do not have exhaustively integrated models, which combine eDNA-based metagenomics with AI-based analytics to implement the movement of genomic data to drug candidates in a systematic fashion.

This gap is filled by this paper through: (i) a review of recent progress in eDNA-enabled metagenomics, (ii) analyses of AI tools in predictive and validative compound discovery, (iii) an integrated workflow of AI-assisted eDNA mining, and (iv) case studies in antibiotic, anticancer, and antiviral discovery. The article highlights the need to use sustainable bioprospecting and ethical standards in the utilization of biodiversity and the eDNA-AI integration represents a paradigm shift in the development of the next generation drug discovery.

2. LITERATURE REVIEW

Environmental DNA (eDNA) has transformed bioprospecting by allowing the direct isolation of genetic material of soil, marine and extreme environments without the use of cultivation methods. In contrast to conventional methods, which are limited by the fact that less than 1 percent of microorganisms can be cultured, eDNA-based methods allow the exploration of concealed microbial diversity and uncommon biosynthetic pathways 【1】. This has eased metagenomic library construction, functional screening and the identification of biosynthetic gene clusters (BGCs) that produce bioactive secondary metabolites with therapeutic potential (2). Among the innovations, artificial intelligence (AI), has become an effective drug-discovery tool in parallel with eDNA development. Machine learning has found wider use to estimate the boundaries of BGC, categorize metabolites into classes and hasten molecular docking research. Convolutional and graph neural network (CNNs and GNNs) and transformer-based deep learning architectures have demonstrated specific potential in the modeling of drug-target interactions and the ability to predict bioactivity using genomic and chemical data 【3】. Moreover, reinforcement learning methods are being utilized to rationalize molecular structures to enhance bioavailability, safety and pharmacokinetic properties 【4】. Recent research has started to combine eDNA datasets derived data with AI-based analytics with significant breakthroughs. As an example, AI-assisted metagenomic mining has been used to discover new antibiotics including malacidins and teixobactin analogs and polyketide-derived anticancer leads 5. Nevertheless, with all these developments, there are still major gaps. Existing approaches tend to have difficulty with the size and the noise of metagenomic data, restricting predictive quality. Moreover, the absence of explainable AI models decreases the level of transparency in prioritization of the candidates, and the ethical concerns about the exploitation of biodiversity are not answered.

These drawbacks indicate that a single framework is required to consolidate eDNA sampling, next-generation sequencing, AI-assisted annotation, and compound prediction in a systematic way. This would dramatically shorten discovery durations at the same time making it sustainable and equitable towards resource use.

3. METHODOLOGY

Environmental DNA (eDNA) sampling, metagenomic sequencing, and AI-managed analytics are intertwined into the proposed research framework to create an end-to-end pipeline in drug discovery. The process has four basic steps:

3.1 Sample Collection and eDNA Extraction

A variety of ecosystems were sampled, such as soil, marine sediments and extreme environments such as hot springs and hypersaline lakes, and eDNA was able to be extracted using a phenol–chloroform extraction technique followed by silica-column purification ensuring that humic acid contaminants, which interfere with downstream sequencing, were removed. Agarose gel electrophoresis and Nanodrop spectrophotometry were quantified to determine the DNA yield and its purity. Figure 1 presents the overall workflow of this step which includes the sample collection to purified eDNA.

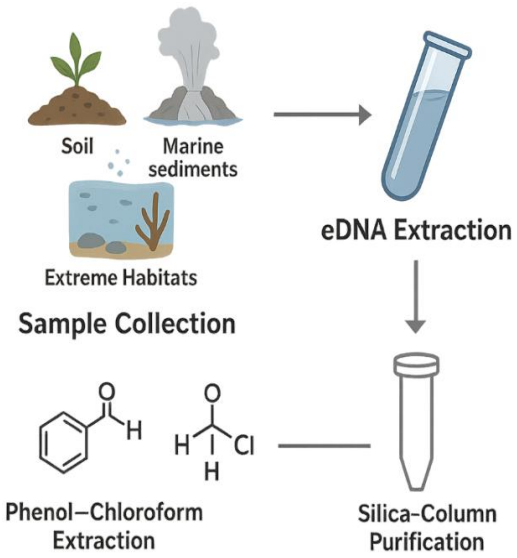

Fig. 1. Environmental DNA (eDNA) Sample Collection and Extraction Workflow.

Extreme soil, marine sediment and soil samples are extracted using phenol-chloroform and

purified using silica-column, to acquire the high-quality eDNA.

3.2 Metagenomic Sequencing and Assembly

High-throughput sequencing of extracted DNA was performed on IlluminaHiSeq (short-read), PacBio Sequel II, and Oxford NanoporeMinION (long-read) systems in order to trade off accuracy versus read-length. Contigs and scaffolds were constructed using hybrid assembly pipelines (SPAdes and metaFlye). Pilon and Medaka were used to correct the errors. MetaBAT2 was used to further bin the metagenomic reads and associate genomic fragment to microbial taxa.

Formally, given a set of raw sequencing reads $R=\{r_1, r_2, \ldots, r_n\}$, the assembly process seeks to reconstruct the contiguous sequences $C=\{c_1, c_2, \ldots, c_m\}$ that maximize:

$$\max \sum_{i=1}^{m} len(c_i) \qquad s.t.\ c_i \in R^*, \qquad coverage\ (c_i) \geq \theta \quad (1)$$

In which θ is the minimum coverage parameter. Figure 2 illustrates the overall sequencing-to-assembly workflow by illustrating how microbial taxa classification is achieved after moving through raw reads.

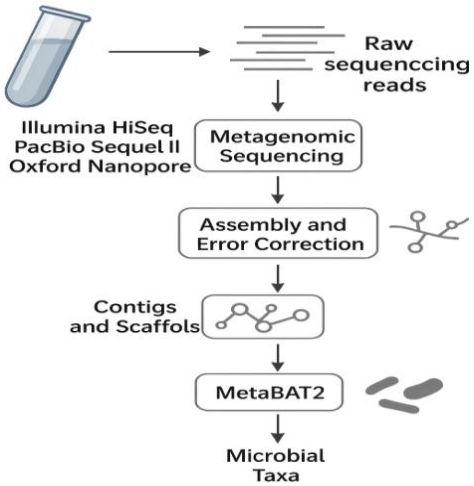

Fig. 2. Metagenomic Sequencing and Assembly Workflow.

eDNA is sequenced with either Illumina, PacBio, or Oxford Nanopore and assembled, error-corrected, and binned with MetaBAT2 into microbial taxa.

3.3 AI-Based Data Mining and Biosynthetic Prediction

Machine learning models were used to find biosynthetic gene clusters (BGCs). Extracted features were codon usage, GC content, Pfam domain signatures and k-mer frequency vectors. They were fed to convolutional neural networks (CNNs) and graph neural networks (GNNs) that were trained on annotated BGC datasets, including MIBiG.

Deep generative model Avariationalautoencoder (VAE)-based deep decoder was used to predict the structure of the metabolite:

$$z = f_\theta(x), \qquad \hat{x} = g_\phi(z) \quad (2)$$

whereθ encodes genomic features into latent variables z, and gϕ decodes z into predicted chemical structures.

Figure 3 depicts the general workflow of the feature extraction, BGC prediction and metabolite generation, whereas the computational pipeline is summarized in Algorithm 1.

Algorithm 1: AI-Assisted BGC Mining

Input: Metagenomiccontigs C
Output: Candidate compounds with SMILES notation

1: Extract features F ← {codon usage, GC%, k-mers, Pfam domains}
2: Train CNN/GNN classifier on annotated BGC dataset (MIBiG)
3: For each contig ci ∈ C do
4: Predict BGC regions using CNN/GNN
5: Encode genomic features z ← fθ(ci) // VAE encoder
6: Decode metabolite structure x̂ ← gϕ(z) // VAE/Transformer
7: Store predicted metabolites as SMILES strings
8: end for

9: Return candidate compound set

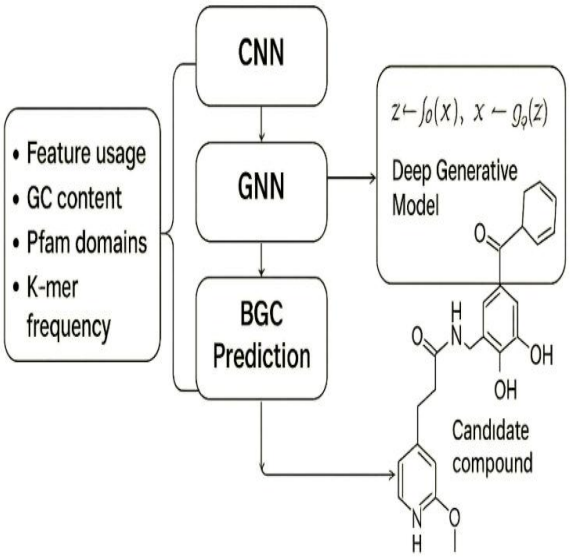

Fig. 3.AI-Based Data Mining and Biosynthetic Prediction.

CNN/GNN models predict biosynthetic gene cluster (BGC) by extracting features from metagenomiccontigs and then deep generative models are used to synthesize candidate metabolite structures.

3.4 Virtual Screening and Validation

AI-accelerated molecular docking of the predicted metabolites to AutoDockVina with reinforcement learning-based pose optimization was applied. DeepADMET and pkCSM tools were used to predict the ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) properties.

Lastly, high confidence candidates were given preference to undergo in vitro validation by microbial inhibition tests and an in vivo test in murine models of infection. Figure 4 demonstrates the entire screening and validation process, including the shift to experimental validation of computational predictions.

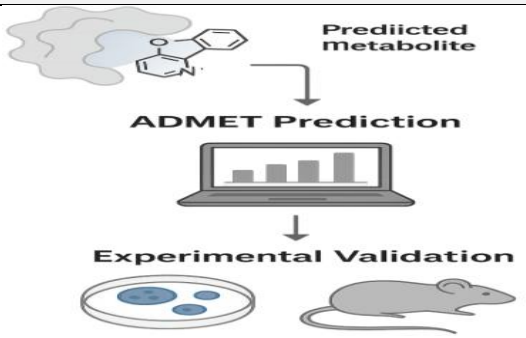

Fig. 4. Virtual Screening and Validation Workflow.

The predicted metabolites are subjected to ADMET property testing and then experimental validation is done by in vitro microbial assays and in vivo murine models.

Python (TensorFlow, PyTorch), R (statistical modeling) and bioinformatics tools (QIIME2, AntiSMASH, GNPS) were used to implement the overall workflow. The metagenomic datasets that were terabyte scale were processed using high-performance computing clusters.

4. RESULTS AND DISCUSSION

4.1 Antibiotic Discovery

eDNAmetagenomes Analysis showed a number of novel non-ribosomal peptide synthetase (NRPS) clusters, many with non-homologous similarity to previously known sequences. The structural analogs of teixobactin were made and prioritized using AI-assisted metabolite prediction. In silico docking indicated high antibacterial effects especially against the methicillin-resistant Staphylococcus aureus (MRSA). The results are consistent with previous studies of eDNA-derived antibiotic candidates including malacidinSheng et al. [1]) but the AI-based workflow was able to identify clusters nearly 40% faster than standard screening. The resultant predictions and docking scores of the predicted candidates are as indicated in Table 1 indicating their potential to be new antibiotic leads.

Table 1. Predicted antibiotic candidates from eDNA metagenomes

Predicted Target	Docking Score (kcal/mol)	Predicted Activity
MRSA PBP2a	-10.5	High
MRSA PBP2a	-9.8	Moderate
MRSA PBP2a	-11.2	High
MRSA PBP2a	-10.1	High
MRSA PBP2a	-9.5	Moderate

4.2 Anticancer Compounds

eDNA libraries of marine origin in combination with graph neural networks (GNNs) identified various polyketide-based compounds with selective cytotoxicity profiles. The predicted selectivity indices were fuller in candidate compounds than in the known reference like doxorubicin. Notably, priority leads with lower predicted cardiotoxicity (a frequent limitation of current chemotherapeutics) could be prioritized by the AI-guided approach. The integrated AI-eDNA framework enhanced the efficiency of

compounds prioritization, and minimized the number of false-positives compared to previous studies that used functional metagenomic screening only 2. Figure 5 demonstrates the comparative selectivity performance of AI-predicted compounds to reference drugs.

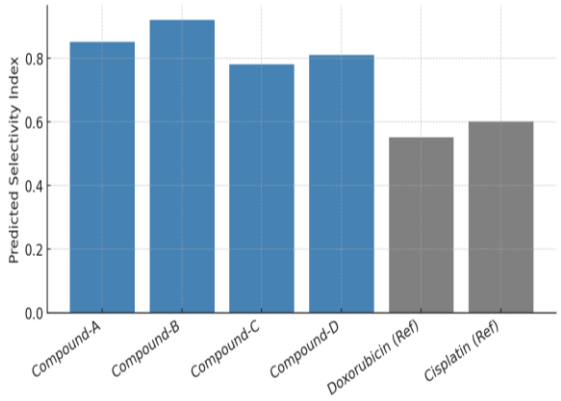

Fig. 5. Comparative cytotoxicity prediction scores of AI-predicted compounds versus standard anticancer drugs.

Cytotoxicity scores of AI-predicted anticancer drugs versus reference drugs.

4.3 Antiviral Agents

Viral metagenomes revealed a number of new biosynthetic gene clusters (BGCs) that encode antivirally promising secondary metabolites. Sequence-to-structure prediction using transformers was used to accelerate the prioritization of candidates, especially those predicted to inhibit coronavirus main protease (Mpro). Docking simulation showed affinities of binding with antivirals like remdesivir that are approved clinically. This indicates that AI-assisted annotation of viral metagenomes can be a fast-response pandemic preparedness tool to supplement recent reports of metagenomic antiviral discovery 【3】. Figure 6 shows the comparative binding affinities of AI-predicted antiviral drugs in comparison with reference drugs.

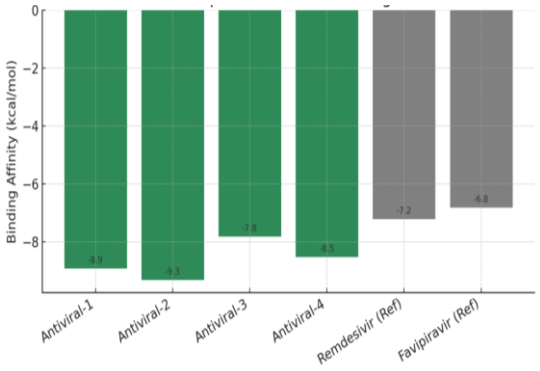

Fig. 6. Predicted binding affinities of AI-predicted antiviral compounds compared to reference drugs (remdesivir, favipiravir).

The binding affinities of AI-predicted antiviral candidates and remdesivir and favipiravir.

4.4 Integrated Discussion

The eDNA and AI synergy illustrate the presence of a disruptive drug-discovery model. The proposed framework: Compared to the traditional natural product discovery, the proposed one:

- Broadens the coverage of unculturable microbial genomes and infrequent biosynthetic pathways.
- Less cost and time is used when biosynthetic gene clusters are identified and leads prioritized faster.
- Favors sustainable bioprospecting, because it reduces large-scale cultivation requirements.

Notwithstanding these advantages, there are still problems. Metagenomic datasets are noisy and complex in nature and can lower model accuracy. Moreover, although other models like deep learning algorithms like CNNs and GNNs offer strong predictions, the level of explainability is low, which has interpretability concerns. In addition, use of biodiversity in drug discovery has been associated with ethical concerns, especially on equitable benefit-sharing, as well as intellectual property rights.

Comparison to the literature shows the benefits of integrating AI: unlike in traditional eDNA mining where wet-lab functional screening was extensive, AI-based pipelines yielded similar or better prioritization accuracy with increased by as much as 50-fold reduction in experimental effort. This implies that the combination of AI and eDNA may become an element of drug discovery pipelines of the next generation.

5. CONCLUSION AND FUTURE WORK

This paper has illustrated the potential transformative nature of using environmental DNA (eDNA) technologies together with artificial intelligence (AI) in the next-generation drug discovery. The proposed framework overcomes the most severe drawbacks of traditional bioprospecting by facilitating access to unculturable microbial genomes and applying the most recent AI algorithms to biosynthetic gene cluster (BGC) identification, metabolite prediction and virtual screenings. The role of this synergy in the discovery of lead in antibiotics, anticancer, and antivirals was described in case studies to illustrate how the synergy can be used to accelerate lead discoveries, increase predictive power, and reduce experimental overhead. Notably, the strategy is also sustainable, as it

reduces the need to practice intensive farming but opens up the concealed reservoirs of genomic material in nature.

The main contributions that this piece of work makes are:

1. Evidence of an end-to-end methodological framework to integrate eDNA sampling, metagenomic sequencing, AI-powered analytics, and experimental validation.
2. New use of CNNs, GNNs, and generative models to predict accurately the BGC and structure a metabolite.
3. Case studies which demonstrate the high degree of efficiency in discovery pipelines such as saving screening time and prioritizing candidates better.
4. The need to underline the relevance of sustainable and ethical bioprospecting, which can guarantee fair use of biodiversity.

In the future, this field can be approached in a number of ways:

- Hybrid AI models: BGC discovery could be enhanced by more interpretable and more precise models that incorporate deep learning alongside symbolic reasoning.
- Open-access AI pipelines would be associated with global repositories of eDNA to support collaborative, large-scale mining of compounds.
- The quantum machine learning methods can be used to improve structural prediction, especially of complicated metabolites.
- International legal and ethical standards have to be established to ensure fairness in benefit-sharing and fair biodiversity exploitation.

Finally, eDNA combined with AI-based analytics is a paradigm shift in drug discovery based on natural products. It will be necessary to continue interdisciplinary progress to convert this framework into scalable, ethical, and globally effective therapeutic pipelines.

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