AI-Driven Molecular Docking in Drug Repurposing: Methodologies, Tools, Case Studies, And Translational Challenges

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***Abstract*—Background and Objective: Drug development is among the most expensive and time-consuming processes in science, costing approximately $2.6 billion and 10–15 years per approved drug, with over 90% of candidates failing before approval. Drug repurposing — identifying new therapeutic uses for existing compounds — offers a faster, lower-cost alternative by leveraging established safety profiles. This review aims to critically evaluate the role of artificial intelligence (AI)-driven molecular docking in accelerating drug repurposing, examining current methodologies, landmark case studies, key databases, and translational challenges.**

Methods: A comprehensive narrative review of peer-reviewed literature was conducted covering five principal AI methodologies: structure-based virtual screening (SBVS) with ML-enhanced scoring functions, ligand-based virtual screening (LBVS) and QSAR modelling, graph neural network (GNN)-based drug-target interaction prediction, AlphaFold 2 and 3-integrated structural proteomics, and knowledge graph/NLP-based network pharmacology. Landmark case studies (baricitinib for COVID-19; halicin as a novel antibiotic) and major databases (DrugBank, ChEMBL, PDB, AlphaFold DB) were systematically reviewed.

Results: AI-driven docking pipelines demonstrate clear superiority over traditional physics-based scoring functions in accuracy and throughput, enabling screening of over 100 million compounds in under 48 hours. AlphaFold 2 and 3 have expanded the druggable proteome to over 200 million predicted structures. Baricitinib, identified via BenevolentAI's knowledge graph, reduced COVID-19 mortality by 38% in randomised trials and achieved WHO standard-of-care status. Halicin, discovered through deep learning, demonstrated novel antibacterial activity against drug-resistant pathogens in vivo. Key limitations identified include data bias, model interpretability (the black-box problem), the AlphaFold docking gap, benchmark reproducibility issues, and a persistent clinical translation gap.

Conclusion: AI-driven molecular docking has transformed drug repurposing from a serendipitous process into a systematic, high-throughput computational strategy with demonstrated clinical impact. Addressing current limitations through explainable AI, federated learning, benchmark standardisation, and integrated computational-experimental workflows will be critical to accelerating the translation of AI-predicted candidates into approved therapies.

***Index Terms*—Drug Repurposing; Molecular Docking; Artificial Intelligence; Virtual Screening; AlphaFold; Graph Neural Networks**

I. INTRODUCTION

Developing new medicines is among the longest and most expensive processes in all of science. The total estimated cost of bringing a new drug to market is approximately $2.6 billion over 10 to 15 years per approved drug, and greater than 90% of all developed drugs never make it to market due to insufficient efficacy, adverse effects, or pharmacokinetic problems [1, 2]. Drug repurposing — also referred to as drug repositioning — provides a highly logical strategy to find new uses for already existing compounds with a history of being safely used in humans. Repurposed agents can reach the market in typically 3–6 years and at significantly lower costs because early toxicology studies and Phase I clinical trials are eliminated. This is especially valuable for neglected diseases and rapid pandemic response [2].

Molecular docking, a critical component of structure-based drug design (SBDD), computationally models the geometry and affinity of small-molecule ligand binding to protein binding sites, enabling rapid in silico prioritization of compound/target pairs prior to experimental validation [3]. Traditional platforms such as AutoDock Vina, Glide, and DOCK6 remain the backbone of SBDD but are limited by scoring function quality and crystal structure availability.

Artificial intelligence (AI) — encompassing machine learning (ML), deep learning (DL), and graph neural networks (GNN) — has made great progress in the field of molecular docking. Training AI scoring functions on large drug-protein interaction datasets has demonstrated clear superiority over rule-based approaches [4]. The introduction of AlphaFold 2 and AlphaFold 3 has greatly expanded accessible targets for docking [5]. This review systematically evaluates the methodological landscape of AI-augmented molecular docking for drug repurposing, covering databases, landmark case studies, challenges, and future directions.

II. BACKGROUND: DRUG REPURPOSING AND MOLECULAR DOCKING

A. Rationale and Costs

The standard drug discovery process has an extremely high failure rate, with less than 10% of Phase I candidates receiving regulatory approval [1]. Drug repurposing circumvents early costly stages because the drug has already been shown safe in humans. The estimated cost to develop a repurposed drug is approximately $300 million compared to more than $2 billion for a new chemical entity [6]. These economic benefits are particularly important for neglected tropical diseases, rare diseases, and rapid pandemic response [2].

B. Principles of Molecular Docking

Molecular docking computationally simulates the binding of a small molecule (ligand) to a receptor — akin to fitting a key into a lock. The process involves: (1) exploration of the conformational, orientational, and positional space of the ligand within the binding pocket; and (2) ranking resulting poses based on predicted binding free energy. Widely used platforms include AutoDock Vina, Glide, DOCK6, and rDock, each differing in search algorithms and scoring methods (empirical, force-field, or knowledge-based). Virtual screening extends docking to library scale, enabling rapid prioritization of hundreds of millions of compounds against a target [7].

C. The Impact of AI on Drug Discovery

ML scoring functions — from random forests to SVMs to deep convolutional networks and GNNs — have shown measurable improvement over classical scoring methods [4, 8]. AI also extends beyond screening to de novo molecular design via generative models (VAEs and GANs), and NLP enables large-scale extraction of drug-target relationships from literature [3]. AlphaFold 2's 3D structural predictions for previously unresolved proteins resolved a critical bottleneck in structure-based drug design [5].

III. AI-DRIVEN METHODOLOGIES IN DRUG REPURPOSING

A. Structure-Based Virtual Screening with AI-Enhanced Scoring

Traditional SBVS methods dock large compound libraries against a target structure and rank resulting poses using a scoring function, historically producing large numbers of false positives. ML-based scoring functions trained on ChEMBL and PDBbind curated affinity datasets outperform physics-based scoring functions. CNNs have produced exceptional performance by directly processing 3D representations of protein-ligand complexes, while DiffDock treats docking as a generative modeling task, estimating the statistical distribution of acceptable binding poses. Recent developments have enabled screening of over 100 million compounds in under 48 hours.

Figure 1 illustrates the complete AI-driven drug repurposing workflow, from large chemical libraries through iterative AI filtering, virtual screening, and ML-enhanced scoring to clinical validation.

B. Ligand-Based Virtual Screening and QSAR Modeling

LBVS relies on the structural and physicochemical characteristics of known active substances when no reliable 3D receptor structure exists. QSAR modelling creates predictive models correlating molecular descriptors to biological activity [7]. Ensemble ML techniques such as random forests and XGBoost effectively handle high-dimensional descriptor spaces,

while GNN-based models achieve state-of-the-art performance on MoleculeNet benchmarks for solubility prediction, hydration free energy estimation, and biological activity classification [4].

C. Graph Neural Networks for Drug-Target Interaction Prediction

GNNs are among the most capable architectures for modelling drug-protein interactions and predicting molecular properties [9]. Because molecular structures are naturally graph-based (atoms as nodes, bonds as edges), GNN architectures capture both local chemical environments and global structural characteristics without the information loss associated with fixed-length vector encoding. DeepDTA combines GNN drug representation with one-dimensional convolutional protein representations, outperforming individual methods on the Davis and KIBA datasets [10]. H2GnnDTI captures multi-scale interaction information and generalises well to new drug-target interactions [11].

D. AlphaFold 2 and AlphaFold 3: Expanding the Druggable Proteome

AlphaFold 2, published in Nature in 2021, predicts protein structures with unprecedented accuracy from amino acid sequence alone, and the AlphaFold Protein Structure Database now provides structural models for over 200 million proteins [5]. The Nobel Prize in Chemistry 2024 recognized this achievement. AlphaFold 3, released in 2024, uses diffusion models for prediction of complex biomolecular assemblies including protein-ligand, protein-nucleic acid, and protein-protein complexes, outperforming available docking tools in the PoseBusters benchmark [12].

E. Knowledge Graphs, NLP, and Network-Based Repurposing

AI technologies for drug repurposing increasingly connect biomedical data types through knowledge graphs reflecting relationships between drugs, targets, diseases, pathways, and clinical outcomes, derived from scientific literature using ML-based Named Entity Recognition (NER) and relationship extraction [3]. Graph embedding techniques generate low-dimensional vector representations enabling predictions about new drug-disease relationships. Network pharmacology uses PPI networks to model disease biology, enabling identification of repurposing candidates that target disease pathways rather than individual proteins [13].

IV. KEY DATABASES AND COMPUTATIONAL RESOURCES

The performance of AI-based docking workflows is strongly dependent on the quality and scope of their underlying databases. The principal resources employed in AI drug repurposing workflows are summarized in Table I.

Table I. Principal Databases in AI-Driven Drug Repurposing

Database	Content & Role
DrugBank	~14,000 drug entries; approved compound libraries and target information.
ChEMBL	>2.5M bioactive compounds; training sets for QSAR/ML models.
PubChem	~119M compounds with biological activity data; large-scale VS campaigns.
ZINC Library	>750M drug-like purchasable compounds; ultra-large library docking.
PDB (RCSB)	~210,000 experimental protein structures; gold-standard receptor inputs.
AlphaFold DB	>200M predicted structures; expands druggable proteome for SBVS.
OMIM/DisGeNET	Disease-gene associations; target prioritization for KG-based repurposing.

V. LANDMARK CASE STUDIES

A. Baricitinib for COVID-19

A landmark example of AI-driven drug repurposing is the identification of baricitinib as a potential COVID-19 treatment [14]. In January 2020, BenevolentAI utilised their proprietary AI-enabled Biomedical Knowledge Graph to identify compounds capable of

interfering with SARS-CoV-2 cell entry and dampening the cytokine storm driving severe COVID-19. The system identified baricitinib — an oral JAK1/JAK2 inhibitor approved for rheumatoid arthritis — as a candidate capable of inhibiting AAK1-mediated viral endocytosis and reducing cytokine-mediated inflammation [14].

In the ACTT-2 randomised trial (n > 1,033), baricitinib combined with remdesivir significantly accelerated hospital discharge and reduced mortality by approximately 35% compared to remdesivir alone [15]. The CoV-BARRIER trial confirmed a 38% reduction in 28-day mortality. Baricitinib subsequently received FDA Emergency Use Authorization and was included in WHO standard-of-care guidelines for severe COVID-19, demonstrating how AI-generated predictions can translate directly into clinical guidelines [15, 16]. The repurposing timeline is illustrated in Figure 2.

B. Halicin: Deep Learning for Novel Antibiotics

Researchers at MIT trained a deep learning model on molecular databases to scan the Drug Repurposing Hub — a curated database of approved and investigational drugs [16]. Halicin, originally investigated for diabetes, was predicted to disrupt the electrochemical gradient across bacterial membranes, representing a novel mechanism of action unlikely to generate conventional resistance. Halicin demonstrated significant antibacterial activity against drug-resistant Acinetobacter baumannii and Mycobacterium tuberculosis both in vitro and in mouse models, establishing AI-driven screening as a pathway to genuinely novel pharmacological mechanisms [16].

C. Oncology and Infectious Disease Agents

Mebendazole, an anthelmintic, was computationally determined to share a tubulin-binding mechanism with anti-tumour agents, with docking studies validating its binding geometry at the colchicine binding site [6]. Celecoxib, a selective COX-2 inhibitor, has been evaluated as an anti-cancer agent in colon, breast, and prostate cancer through AI-assisted target identification [6]. Oseltamivir, darunavir, raltegravir, and chloroquine have each been investigated against multiple infectious disease targets using AI-based analytical methods [6].

VI. COMPARATIVE METHODOLOGICAL OVERVIEW

A systematic comparison of the principal AI-based methodologies for drug repurposing is presented in Table II.

Table II. Comparative Overview of AI-Driven Methodologies

Approach	Key Tools	Strengths	Limitations
SBVS	AutoDock Vina, DiffDock	Mechanistic insight; uses 3D structure	Needs crystal structures; slow for huge libraries
LBVS / QSAR	RF, SVM, XGBoost	No structure needed; rapid	Limited by known ligand data
ML Scoring	CNN, Graph Attention Nets	Improved accuracy; fewer false positives	Overfitting; low interpretability
GNN-DTI	DeepDTA, H2GnnDTI	Graph topology; multi-relational	Needs high-quality training data
AlphaFold-Integrated	AF2+AutoDock; AF3	Expands druggable proteome	May underperform without refinement

VII. CHALLENGES AND LIMITATIONS

Despite remarkable progress, several persistent challenges limit the real-world translation of AI-driven drug repurposing pipelines, summarized in Table III.

Table III. Key Challenges in AI-Driven Drug Repurposing

Challenge	Description
Data Quality & Imbalance	ChEMBL and similar databases have unequal representation of target classes and chemical scaffolds, producing biased model predictions [7].
Black-Box Interpretability	Deep learning models achieve high performance without transparency. SHAP and LIME provide post-hoc attribution, but biological rationale is often unclear [17].
AlphaFold Docking Gap	AF2 structures frequently underperform PDB structures in docking without side-chain refinement. AF3 shows improvement but needs further validation [5, 12].
Benchmark Reproducibility	DUD-E and Davis datasets exhibit proximity bias and train-test leakage that overestimate prospective screening performance [18].
Clinical Translation Gap	Most computationally predicted candidates fail in biochemical assays due to imprecise scoring functions, incomplete ADMET predictions, and protein flexibility issues.

VIII. FUTURE DIRECTIONS

A. Multimodal Data Integration

Future repurposing projects integrating multi-omics data will establish predictive models supporting multi-modal repurposing based on disease biology rather than binding affinity alone. Biomedical foundation models offer new ways to integrate transcriptomic, proteomic, and metabolomic data.

B. Explainable AI and Regulatory Compatibility

As AI-derived repurposing agents advance toward clinical trials, regulatory frameworks at FDA and EMA will increasingly require mechanistic reasoning to support computational evidence — specifying which protein-ligand binding events occur, which pathways are modulated, and what molecular properties drove identification [17].

C. Federated Learning and Quantum Computing

Federated learning enables collaborative AI model development across institutions while preserving patient privacy and proprietary rights [19]. Quantum computing may enable evaluation of protein-ligand free energy at quantum mechanical precision via variational quantum eigensolvers (VQEs) and hybrid quantum-classical methods within the next decade [4].

D. Real-Time Adaptive Screening Pipelines

Active learning systems iteratively retrain AI models on experimental screening results, directing subsequent efforts toward regions of highest predicted activity [20]. Closed-loop approaches integrating AI prediction, automated synthesis, and high-throughput biochemical assay have potential to compress hypothesis-to-validation timelines from years to months.

IX. CONCLUSION

AI-based molecular docking represents one of the most rapidly developing and impactful areas within computational pharmacology. With ML-based scoring functions, GNN-based DTI prediction, generative molecular modelling, and AlphaFold-based structural proteomics, today's AI-accelerated molecular docking pipelines offer unprecedented high-throughput exploration of vast chemical and biological spaces.

The case of baricitinib — from a BenevolentAI knowledge graph query to a WHO Standard-of-Care recommendation — demonstrates that AI-driven drug repurposing is a viable strategy for clinical drug development. Halicin establishes that AI-driven screening can identify entirely novel pharmacological mechanisms. Persistent challenges — data bias, model opacity, the AlphaFold docking gap, benchmark reproducibility, and the clinical translation gap — require investment in benchmark standardisation, explainable AI architectures, federated data sharing, and integrated computational-experimental workflows.

The future of drug repurposing will be built on multi-modal AI-powered pipelines, quantum simulation, and

adaptive real-time screening rather than serendipitous observation or exhaustive experimental testing alone.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

USE OF GENERATIVE AI AND AI-ASSISTED TOOLS

The author used Claude (Anthropic) to assist with manuscript drafting, structural formatting, and language refinement. Figures were created using BioRender (biorender.com). The intellectual responsibility for all content, analysis, and conclusions remains entirely with the author.

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FIGURES

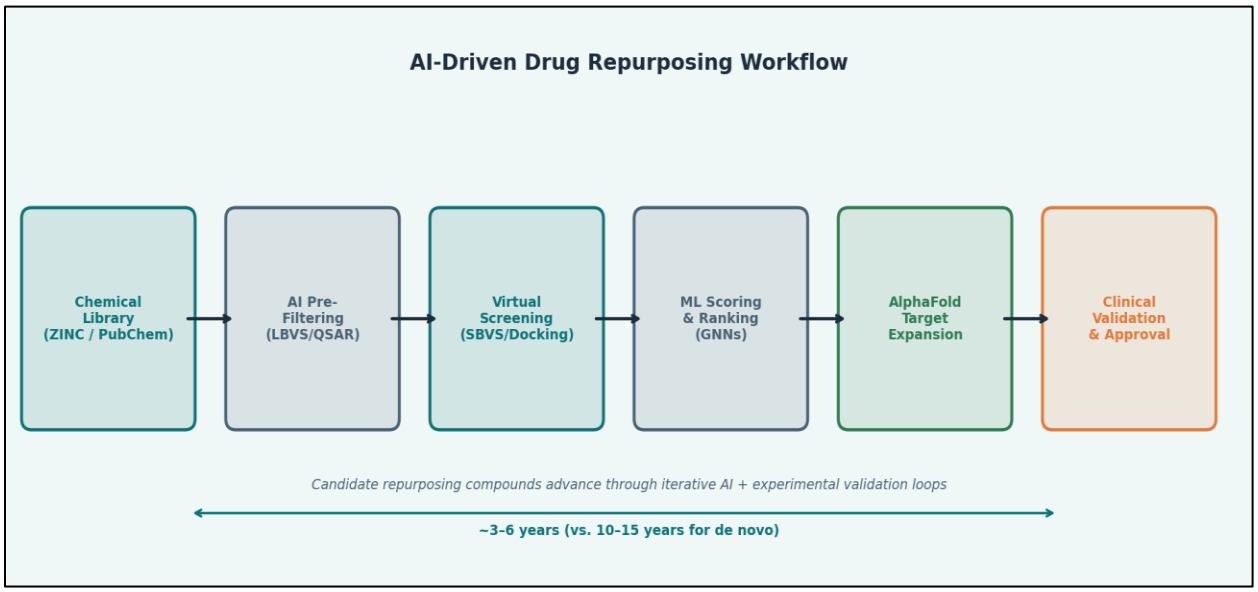

Fig. 1. AI-driven drug repurposing workflow — from large chemical libraries through iterative AI filtering, virtual screening, and ML-enhanced scoring to clinical validation, compressing the development timeline from 10–15 years to 3–6 years. Figure created using BioRender (biorender.com).

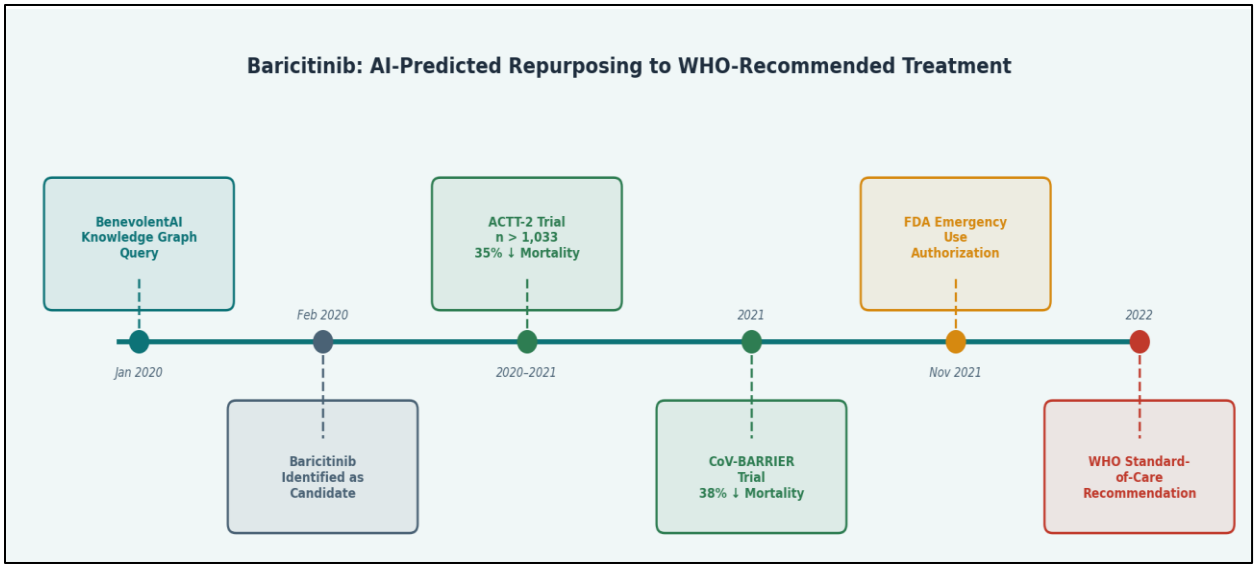

Fig. 2. Baricitinib repurposing timeline — from BenevolentAI knowledge graph identification in January 2020 through FDA Emergency Use Authorization and WHO standard-of-care recommendation, illustrating the speed of AI-enabled translational drug repurposing. Figure created using BioRender (biorender.com).