AI - DRIVEN DRUG REPURPOSING METHODOLOGY FOR SELECTING THE LEAD COMBINATION OF DRUGS FOR VARIOUS DISEASES

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Abstract

Artificial intelligence (AI) and machine learning (ML) provide powerful computational tools for integrating heterogeneous biomedical data and identifying clinically relevant drug-disease and drug-target relationships. The present review focuses on an AI-driven drug repurposing methodology for selecting lead combinations of drugs for various diseases. The methodology encompasses disease characterization, integration of genomic and multi-omics data, identification of novel biomolecular targets, prediction of drug-target interactions, and prioritization of existing drugs for potential repurposing. Particular emphasis is placed on AI-based prediction of drug synergism and antagonism, where molecular targets, biological pathways, drug-response profiles, pharmacological characteristics, and drug-drug interaction data can be integrated to identify promising combinations. The application of AI in personalized medicine, pharmaceutical product development, clinical trial design, and combination drug delivery is also discussed. A systematic multi-parameter approach incorporating therapeutic potential, target complementarity, predicted synergy, safety, pharmacokinetic compatibility, and available clinical evidence can facilitate the selection of lead drug combinations for subsequent experimental validation. Despite its potential, challenges related to data quality, model interpretability, validation, bias, and clinical translation remain. Overall, AI-driven drug repurposing represents a promising framework for accelerating the rational discovery of effective drug combinations and supporting the development of precision and personalized therapeutic strategies for complex diseases.

Keywords: *Drug Repurposing, Drug Development, Explainable Artificial Intelligence, Heart Failure, Drug Discovery*

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1. Introduction

Drug discovery and development is a complex, time-consuming, and costly process involving target identification, lead discovery, preclinical evaluation, clinical trials, and regulatory approval. The high incidence of drug candidate attrition throughout development has prompted researchers to look at several strategies that might shorten the time, expense, and risk of development. One such tactic is drug repurposing, often referred to as drug repositioning or reprofiling, which entails finding novel therapeutic uses for already available medications that have previously been authorised or studied for different purposes. This strategy may hasten the creation of treatments for illnesses with few available treatments as many repurposable medications already have knowledge about pharmacokinetics, pharmacodynamics, toxicity, dose, and manufacture. (Bakhtiari et al., 2026; Ghandikota & Jegga, 2024).

A key technical element of contemporary medication repurposing is artificial intelligence (AI). Large and diverse datasets may be processed using machine learning (ML) and deep learning (DL) algorithms to find intricate links that might not be obvious using traditional statistical or experimental methods. Drug-target interaction prediction, drug-disease association prediction, molecular representation learning, knowledge-graph reasoning, natural language processing, network analysis, and the integration of multi-omics and clinical data are among the applications of AI-driven repurposing techniques. These methods may increase the effectiveness of the drug repurposing process and help prioritise current medications based on their anticipated therapeutic relevance (Ghandikota & Jegga, 2024; Bakhtiari et al., 2026).

Many complicated disorders are characterised by the simultaneous dysregulation of numerous molecular targets and biological pathways, notwithstanding the importance of identifying unique repurposable therapies. As a result, focusing on only one disease mechanism might not always result in a sufficient treatment response. By concurrently modifying many targets or pathways, drug combination treatment offers an alternate strategy and may result in additive or synergistic therapeutic benefits. However, comprehensive experimental screening is nearly impossible since the number of potential medication combinations grows exponentially with the number of pharmaceuticals accessible. Therefore, by giving priority to pairings with a higher likelihood of therapeutic synergy, computational techniques can minimise the search space (Sun et al., 2018; Kumar et al., 2022).

Therefore, choosing a lead drug combination may be structured as a multi-stage computational decision-making process for an AI-driven drug repurposing technique. First, a disease-specific molecular profile may be established using genes, proteins, pathways, phenotypes, and clinical features linked to the condition. The targets, modes of action, chemical structures, molecular signatures, safety profiles, and clinical data of already available medications may then be used to characterise them. A prioritised pool of candidate medications may be produced by using AI and ML algorithms to anticipate possible drug-disease connections. Drug-target networks, route complementarity, molecular similarity, projected synergy, drug-drug interaction data, toxicity, and existing clinical evidence may then be used to assess the most promising candidates in combination (Fu et al., 2026; Ghandikota & Jegga, 2024).

Because a computationally predicted combination must meet several requirements rather than only exhibiting a high projected synergy score, the lead combination selection stage is very crucial. Complementary modes of action, adequate disease relevance, acceptable safety and drug-drug interaction profiles, pharmacological feasibility, and corroborating experimental or clinical data are all necessary for an excellent combination. To anticipate the synergistic, additive, or antagonistic effects of untested medication pairings, machine learning models may be trained with experimentally recorded combination-response datasets. The number of combinations that need further laboratory research can be greatly decreased by using such computational prioritisation (Kumar et al., 2022; Li et al., 2023).

Therefore, a methodical framework that incorporates pharmacology, artificial intelligence, machine learning, network medicine, systems biology, bioinformatics, and clinical evidence may be provided by an AI-driven medication repurposing approach for choosing lead drug combinations for different illnesses. The creation of such an integrated methodology could aid in the reduction of the vast search space related to drug combinations, enhance the logical selection of promising therapeutic candidates, and ease the shift from computational prediction to clinically and experimentally relevant drug-repurposing strategies.

1.2 The Challenges of Traditional Drug Discovery

A therapeutic candidate must be gradually identified and optimised before undergoing a thorough preclinical and clinical review in the lengthy, complicated, costly, and risky process of traditional drug development. Target discovery and validation, hit identification, lead optimisation, preclinical research, clinical development, regulatory review, and post-

marketing surveillance are all often included in the traditional process. The overall productivity of pharmaceutical research and development is still limited by high attrition, lengthy development timelines, and rising costs, despite advancements in molecular biology, medicinal chemistry, pharmacology, and screening technologies that have improved the ability to identify potential drug candidates (Paul et al., 2010; Pammolli et al., 2011).

The length of time needed to create a novel therapeutic agent is one of the main drawbacks of conventional drug research. Years of research may end if a candidate fails any of the multiple successive steps that they must go through. In order to assess safety, dose, pharmacokinetics, effectiveness, and comparative therapeutic benefit, clinical development entails several stages. Longer development durations are also a result of the growing complexity and expense of clinical research, especially in Phases II and III (Pammolli et al., 2011; Frantz, 2003).

Another significant issue is high financial expenditures. Laboratory research, medicinal chemistry, animal studies, clinical trials, regulatory actions, manufacturing, and infrastructure all require large investments in order to produce new drugs. Crucially, the total cost of successfully created medications eventually includes the cost of failed candidates. The capitalised pre-launch research and development cost of a successful new molecular entity ranged from roughly US$161 million to US$4.54 billion, depending on the methodology, therapeutic area, development period, and components included in the calculation, according to a systematic evaluation of published estimates (Wouters et al., 2021).

Traditional drug discovery is also affected by **poor pharmacokinetic and pharmacological properties**. A promising molecule may exhibit inadequate absorption, distribution, metabolism, excretion, or toxicity (ADMET) characteristics, limiting its ability to reach the intended biological target at an effective concentration. Although modern drug-design and formulation technologies have improved the early identification and management of such problems, ADME and safety-related issues continue to contribute to attrition during drug development (Kenakin, 2024).

The main drawbacks of classical drug discovery are its high cost, long development time, significant attrition, biological complexity, unclear clinical translation, and challenges in assessing various therapeutic pathways. Alternative approaches that can make use of current pharmacological knowledge and minimise needless early-stage development are desperately needed as a result of these difficulties. Because current medications may be methodically

assessed for novel therapeutic indications using collected molecular, pharmacological, and clinical information, drug repurposing—especially when paired with artificial intelligence and machine learning—offers a compelling alternative. By finding possible medication combinations and ranking lead combinations based on anticipated effectiveness, synergistic mechanisms, safety, and disease relevance, AI-driven methods might further expand this idea. Refer to Figure 1.

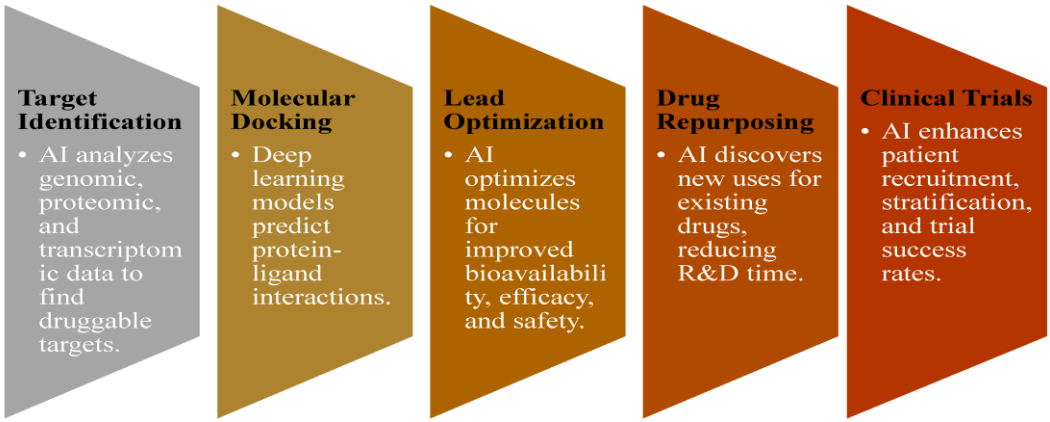

Figure 1. AI-Driven workflow in drug discovery

1.3. The importance of AI in personalized medicine

In addition to speeding up traditional drug development, artificial intelligence (AI) has become a potent tool in precision and personalised medicine, allowing treatment approaches to be customised based on unique clinical, biochemical, and genetic traits. Disease causes, therapeutic responsiveness, treatment efficacy, and sensitivity to side effects can all differ significantly amongst patients with the same illness. By combining sizable and intricate datasets from genomes, transcriptomics, proteomics, metabolomics, clinical records, and other patient-specific data, AI-based methods may address this heterogeneity. More accurate therapeutic decision-making is supported by the discovery of molecular patterns and biomarkers linked to treatment response through the analysis of these multidimensional datasets (Johnson et al., 2021; Topol, 2019).

Identification of patient-specific therapy responses is made possible by the combination of machine learning and deep learning algorithms with multi-omics data. AI models are able to identify intricate connections between pharmacological targets, biological pathways, genetic variations, and clinical characteristics that could be difficult to find using traditional analytical techniques. According to Rajkomar et al. (2019) and Vamathevan et al. (2019), these methods can thus help forecast treatment success, identify patients who are more likely

to respond to a certain medication, and reduce the risk of ineffective treatment or adverse drug responses. Figure 2 shows how AI may be used to integrate various biological data sources and enable individualised treatment decisions.

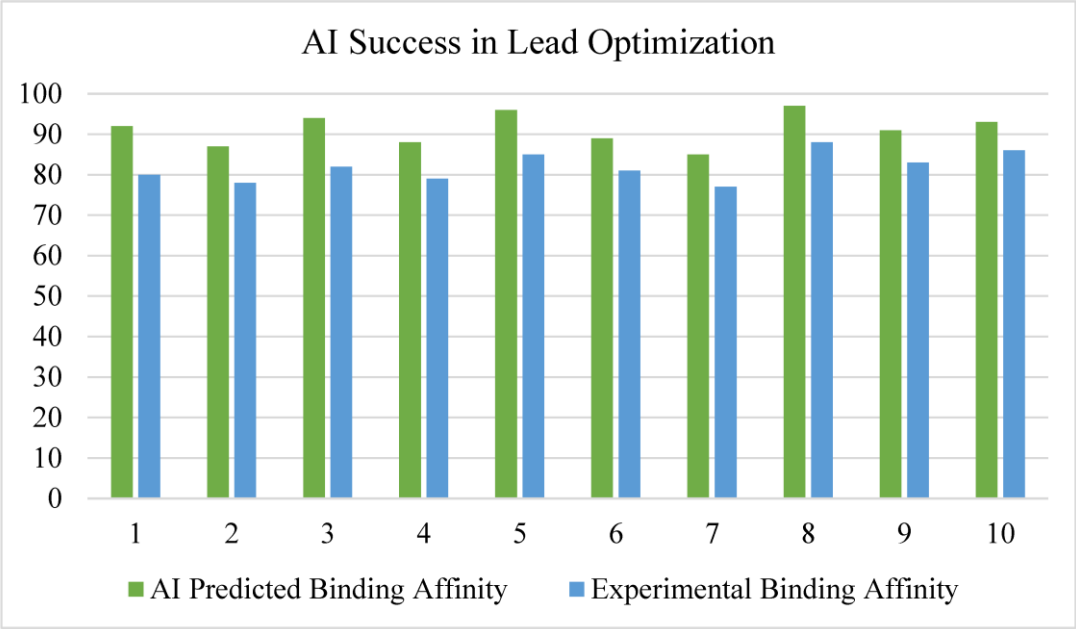

Figure 2. AI Success in Lead Optimization

The developing subject of computational pharmacology, which uses computational techniques to comprehend drug action, drug response, and patient-specific pharmacological features, is strongly related to personalised medicine. To help choose potentially effective treatment medicines, AI may combine molecular biomarkers with drug-target interactions, pharmacokinetic and pharmacodynamic data, disease-associated pathways, and clinical features. According to Johnson et al. (2021) and Topol (2019), this method allows medication development and treatment methods to shift from population-level forecasts to more customised therapeutic treatments.

AI-based computational pharmacology is also particularly relevant to drug repurposing, as existing drugs can be evaluated against patient-specific molecular signatures to identify alternative therapeutic applications. Rather than considering a drug as universally effective for a particular disease, AI models can help determine whether a drug is likely to be beneficial for a specific molecular or clinical subgroup. This creates an important connection between personalized medicine and AI-driven drug repurposing, in which patient characteristics can be incorporated into the prioritization of repurposable candidates (Ghandikota & Jegga, 2024; Fu et al., 2026). The relationship between different biomedical

data types and their potential applications in AI-assisted personalized medicine is presented in Figure 3.

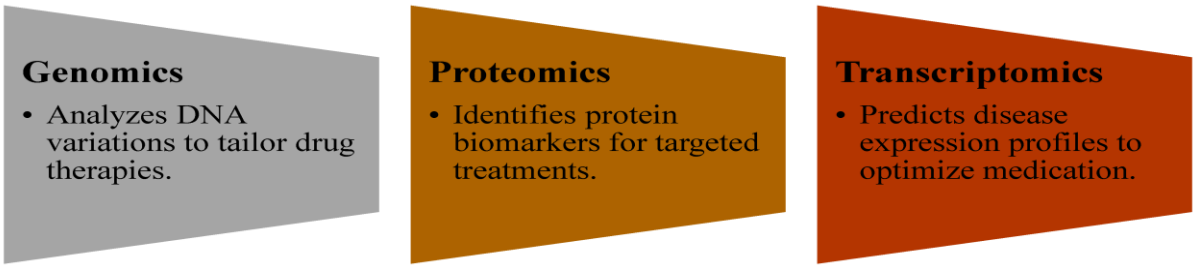

Figure 3. Data Type and the Role of AI.

1.4. AI-Powered approaches in drug discovery

Protein structure prediction is one of the main uses of AI in contemporary drug research. By providing very precise prediction of protein three-dimensional structures from amino acid sequences, DeepMind's deep-learning-based system AlphaFold marked a significant advancement in computational structural biology. Because structural data can shed light on binding locations, chemical interactions, and possible drug action processes, it is essential to rational drug development. Thus, the availability of predicted protein structures can help in virtual screening, drug-target interaction analysis, and structure-based drug design (Jumper et al., 2021).

Drug repurposing can also benefit from AI-driven structural prediction, especially when structural data is integrated with virtual screening, drug-target network analysis, and molecular docking. To find newly undiscovered interactions, current medications can be computationally assessed against disease-associated proteins. According to Ghandikota and Jegga (2024), these methods can produce novel theories about the ways in which well-known medications could have therapeutic benefits in different disease indications.

For the present research framework, AI is particularly important because the objective extends beyond identifying a single candidate drug. The methodology aims to identify lead combinations of repurposed drugs for different diseases. This requires the integration of multiple layers of information, including disease-associated genes and proteins, drug-target interactions, molecular pathways, pharmacological mechanisms, drug-drug interactions, safety information, and predicted combination efficacy. AI and machine-learning models can integrate these heterogeneous data sources and rank candidate drug combinations according to multiple parameters rather than relying on a single molecular interaction.

Disease characterisation, target identification, data integration, candidate drug identification, drug-target prediction, repurposing prediction, drug-combination generation, synergy prediction, safety assessment, and lead-combination prioritisation are all steps in the progressive workflow of AI-powered drug discovery and repurposing. In addition to lowering the number of possibilities requiring in-depth experimental research, such an integrated computational framework offers the potential to speed up the discovery of viable treatment combinations. Figure 4 shows a conceptual comparison between traditional and AI-assisted drug development methods.

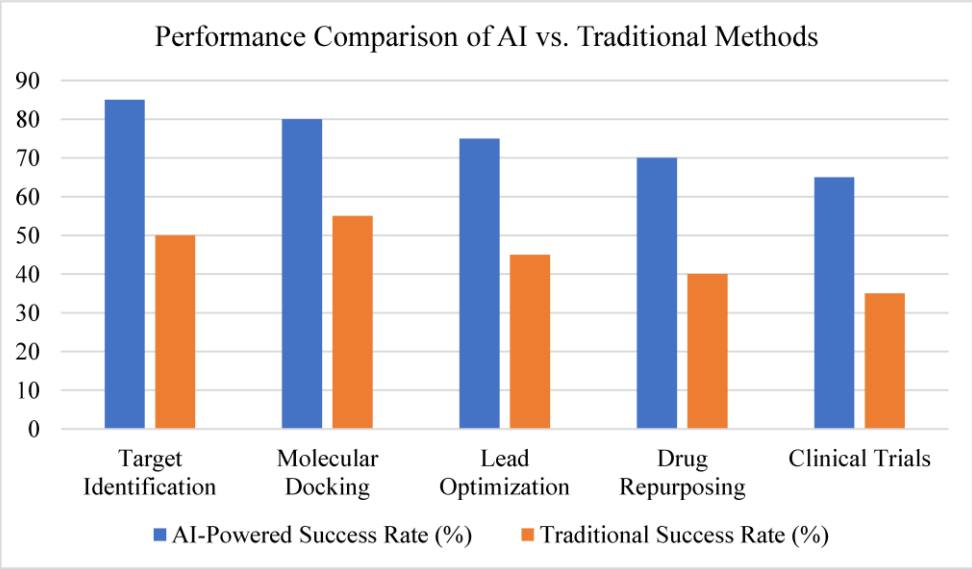

Figure 4. Performance comparison of AI vs. Traditional methods

1.5 Application of AI Algorithms for Drug Repurposing

One potential method for finding new therapeutic uses for currently available medications is the application of artificial intelligence (AI) algorithms to drug repurposing. Drug repurposing makes use of previously characterised medications and their collected pharmacological, toxicological, and clinical data, in contrast to traditional drug development, which often starts with the identification and optimisation of novel chemical entities. By combining diverse biomedical information and discovering hitherto unknown connections between medications, molecular targets, biological processes, and illnesses, artificial intelligence (AI) can expedite this process (Ghandikota & Jegga, 2024; Fu et al., 2026).

The capacity of AI-based medication repurposing to handle massive, multidimensional datasets is one of its main advantages. Drug-target interactions, disease-associated genes, protein-protein interactions, gene-expression profiles, molecular structures, clinical records,

databases of adverse events, electronic health records, scientific literature, and multi-omics data are some examples of these datasets. These datasets can have significant patterns extracted by machine learning (ML) and deep learning (DL) algorithms, which can then be used to forecast possible drug-disease connections. The number of candidates that need to be evaluated experimentally can be significantly decreased by using this computational method (Vamathevan et al., 2019; Ghandikota & Jegga, 2024).

1.5.1. Machine Learning-Based Drug-Disease Association Prediction

Machine learning algorithms are widely used to predict whether an existing drug may have therapeutic potential against a particular disease. Supervised learning methods can be trained using known drug-disease associations, whereas unsupervised and semi-supervised approaches can identify hidden relationships within biological datasets. Commonly applied algorithms include **random forests, support vector machines, logistic regression, gradient boosting, and neural networks**. These models can use molecular descriptors, drug targets, disease-associated genes, pathways, and phenotypic characteristics as input features to generate drug-repurposing predictions (Vamathevan et al., 2019; Bakhtiari et al., 2026).

1.5.2. Deep Learning for Drug Repurposing

Deep learning provides greater capacity for learning complex nonlinear relationships within high-dimensional biomedical data. Convolutional neural networks, recurrent neural networks, autoencoders, and transformer-based architectures have been applied to molecular representation, drug-target prediction, drug-disease association, and biomedical text mining. Deep-learning models can learn informative representations directly from molecular structures or biological profiles, potentially reducing dependence on manually engineered features. These approaches have expanded the ability to identify complex relationships that may be overlooked using conventional computational methods (Bakhtiari et al., 2026).

1.5.3. Graph Neural Networks and Knowledge Graphs

Many drug-repurposing problems can naturally be represented as networks because drugs, diseases, genes, proteins, pathways, and adverse events are interconnected. Knowledge graphs (KGs) provide a structured representation of these relationships, while graph neural networks (GNNs) can learn from the topology and attributes of such networks. AI models can use these approaches to identify missing links between drugs and diseases and predict novel

therapeutic associations. The integration of knowledge graphs with GNNs has therefore become an important direction in computational drug repurposing (Fu et al., 2026; Bakhtiari et al., 2026).

1.5.4. AI-Based Analysis of Gene-Expression Signatures

Gene-expression data provide another important source of information for drug repurposing. Disease-associated transcriptional signatures can be compared with drug-induced gene-expression signatures to identify compounds capable of reversing or normalizing disease-associated molecular changes. AI and machine-learning approaches can improve the interpretation of these high-dimensional expression profiles and prioritize drugs according to their predicted ability to modulate disease-related pathways. This approach is particularly useful when the molecular mechanism of a disease is complex or involves multiple dysregulated genes.

1.5.5. Structure-Based AI and Molecular Interaction Prediction

AI algorithms can also be applied to **drug-target interaction (DTI) prediction** and structure-based drug repurposing. Molecular descriptors, chemical structures, protein sequences, and predicted three-dimensional protein structures can be integrated into computational models to estimate the likelihood of interactions between existing drugs and disease-associated targets. Advances in protein structure prediction, including AlphaFold, have expanded the availability of structural information that can be incorporated into computational drug-discovery and repurposing workflows (Jumper et al., 2021).

1.5.6. Natural Language Processing for Drug Repurposing

The scientific literature contains a vast amount of information regarding drug mechanisms, disease biology, clinical observations, adverse reactions, and potential therapeutic relationships. **Natural language processing (NLP)** and transformer-based language models can process scientific publications, patents, clinical-trial records, and electronic health records to extract drug-disease, drug-target, and drug-drug relationships. This enables previously fragmented information to be converted into structured knowledge that can subsequently be incorporated into AI-driven repurposing models (Ghandikota & Jegga, 2024).

1.5.7. AI for Drug Combination Repurposing

An important extension of AI-driven drug repurposing is the identification of **effective combinations of existing drugs**. In complex diseases, simultaneous modulation of multiple molecular pathways may provide greater therapeutic benefit than targeting a single pathway. However, the number of possible drug combinations is extremely large, making exhaustive experimental screening impractical. AI algorithms can integrate drug-target networks, molecular signatures, pathway relationships, chemical characteristics, and experimentally measured drug-combination responses to predict potential synergistic combinations (Kumar et al., 2022; Li et al., 2023).

In the context of the present methodology, candidate combinations can initially be generated from individually prioritized repurposable drugs. AI models can then evaluate each combination according to mechanistic complementarity, predicted synergy, disease-pathway coverage, drug-drug interactions, toxicity, pharmacokinetic compatibility, and existing clinical evidence. A multi-parameter scoring system can subsequently be used to rank combinations and identify the most promising lead drug combination for further validation.

1.5.8. Multi-Omics Integration and Precision Repurposing

A more complete picture of disease biology is produced by combining genomes, transcriptomics, proteomics, metabolomics, and clinical data. These many data layers may be integrated by AI systems to predict therapy responses and identify molecular subtypes. This method makes it possible for drug repurposing to advance toward precision repurposing, where a drug or drug combination is chosen based on the molecular features of a specific disease or patient subgroup rather than just the traditional disease classification (Johnson et al., 2021; Fu et al., 2026).

Overall, by facilitating candidate identification, drug-target prediction, disease association prediction, molecular signature analysis, knowledge-graph reasoning, drug-combination prediction, synergy assessment, and lead prioritisation, AI algorithms offer a thorough computational framework for drug repurposing. By combining these methods, medication repurposing can become a methodical, data-driven approach rather than a process that is mostly hypothesis-driven. The ultimate goal of the suggested methodology is to integrate these AI capabilities into a single workflow that can choose the most promising lead

combination of repurposed medications for various diseases while concurrently taking safety, clinical viability, therapeutic efficacy, and synergistic potential into account.

1.6. Transforming Side Effects into Therapeutic Opportunities

Adverse drug responses are a significant factor in both drug research and clinical practice since they are typically thought of as unwanted outcomes of pharmacological therapy. However, there is growing evidence that the biological consequences causing certain adverse outcomes may also provide important details about therapeutic actions that were previously unknown. An apparent adverse effect may occasionally indicate an off-target pharmacological action that may be therapeutically beneficial in another condition since many medications interact with various molecular targets and biological pathways. According to Ashburn and Thor (2004) and Oprea and Mestres (2012), this idea offers a crucial mechanistic basis for drug repurposing, which is the process of evaluating an existing medication for a new application based on its known or recently discovered biological effects.

The examination of drug-induced adverse-event profiles is a significant source of information for repurposing. Molecular targets, biological pathways, or pharmacological processes may be shared by medications that exhibit comparable adverse-event patterns. On the other hand, an adverse event linked to one medication may indicate a possible therapeutic impact in a condition with the opposite biological mechanism. These findings can be developed into theories for novel therapeutic uses. For instance, correlations between drug exposure and illness outcomes can be found in epidemiological and pharmacovigilance data, which may then be examined using molecular and experimental methods (Sirota et al., 2011; Lounkine et al., 2012).

Large pharmacological and clinical datasets may now be systematically analysed thanks to computational technologies, which have significantly enhanced this approach. Information from medicine labels, adverse-event databases, electronic health records, biological literature, drug-target interaction databases, and molecular networks may all be integrated via artificial intelligence (AI) and machine learning (ML). These algorithms are able to rate possible repurposing candidates after discovering subtle connections between adverse events, medications, targets, and illnesses. According to Ghandikota and Jegga (2024), AI can

thereby turn isolated observations of unexpected medication effects into testable ideas for therapeutic repurposing.

The phenotypic resemblance between pharmacological effects and illness presentations is a particularly helpful tactic. To ascertain if a medicine may alter a biological process pertinent to another illness, clinical phenotypes produced by drug exposure might be compared with disease phenotypes. Therefore, medications whose known effects coincide with or counteract disease-associated phenotypes can be found using computational phenotype-based techniques. These methods are particularly useful when disease processes include numerous interrelated pathways or when molecular targets are poorly defined.

Combining such data with knowledge graphs makes AI very useful. Drugs can be linked to their targets, side effects, illnesses, pathways, genes, and clinical observations using a knowledge graph. Then, missing or previously unknown links within the network can be found using machine-learning and graph-based methods. For example, a drug-associated adverse event may be connected through shared molecular pathways to a disease phenotype, generating a hypothesis that the drug could potentially influence that disease. This approach enables repurposing predictions to be derived from relationships across multiple biological and clinical data sources rather than from a single dataset (Fu et al., 2026).

Thus, one important aspect of contemporary medication repurposing is the conversion of adverse effects into therapeutic prospects. Unexpected pharmacological effects might be viewed as biological cues that disclose new mechanisms of drug action rather from being only viewed as liabilities. These hints may be transformed into methodical repurposing hypotheses through the integration of pharmacovigilance data, phenotypic information, molecular networks, and AI-based analytical techniques. Side-effect profiles can therefore function as an extra layer of evidence for candidate selection, mechanism discovery, safety evaluation, and prioritisation of synergistic drug combinations within an AI-driven approach for choosing lead medication combinations.

1.7 Identifying Novel Biomolecular Targets for Existing Drugs

Finding new biomolecular targets for current medications is one of the core ideas of AI-driven drug repurposing. A drug's whole pharmacological activity may comprise interactions with several proteins, enzymes, receptors, transporters, ion channels, and signalling

pathways, even though it is often formulated against a certain primary target or therapeutic mechanism. Opportunities for therapeutic use in illnesses other than the initial indication may arise from these new interactions, which may be the cause of biological effects that were previously unknown. Therefore, a crucial step in increasing the therapeutic potential of already available medications is the comprehensive discovery of hitherto unidentified or understudied drug-target associations (Ashburn & Thor, 2004; Oprea & Mestres, 2012).

Ligand-based target prediction is a significant computational approach that compares an existing drug's chemical structure to known ligands linked to various molecular targets. Proteins that may interact with the medication can be identified using structural similarities, molecular fingerprints, pharmacophore features, and computed molecular descriptors. The fundamental idea is that molecules with similar structures might have comparable biological functions. By discovering nonlinear correlations between molecular characteristics and target activity, AI models can expand on this idea and enhance the ranking of possible new targets.

Structure-based drug-target prediction is another crucial strategy. This method compares a drug's molecular structure to the three-dimensional structure of possible protein targets. While AI-based scoring methods can enhance the prioritisation of possible contacts, molecular docking and virtual screening can predict binding modes and binding affinities. The amount of proteins for which structural information may be computationally examined has significantly increased thanks to developments in protein structure prediction, especially the creation of AlphaFold (Jumper et al., 2021). This opens up new possibilities for testing current medications against proteins linked to illness that weren't taken into account during the initial drug-development phase.

Another crucial method for finding new biomolecular targets is network-based techniques. Drugs, proteins, genes, illnesses, pathways, and phenotypes may all be represented as linked networks in biological systems. Even if only one target was initially identified, a medication may affect several proteins inside such a network. Proteins that occupy physiologically significant locations close to known drug targets or genes linked to illness can be found using network-based algorithms. This offers a systems-level view of drug action and makes it possible to forecast indirect or hitherto unknown drug-target connections (Oprea & Mestres, 2012).

The incorporation of knowledge graphs has further enhanced target discovery in drug repurposing. A biomedical knowledge graph can integrate relationships among drugs,

proteins, genes, diseases, pathways, phenotypes, adverse effects, and clinical observations. AI and graph-based learning algorithms can analyze these relationships and predict missing links within the network. For example, if an existing drug is connected to several proteins involved in a disease-associated pathway, a graph-based model may identify an additional protein that represents a plausible but previously unrecognized target. Such predictions can subsequently be investigated experimentally (Fu et al., 2026).

Finding new biomolecular targets is also very important for polypharmacology and choosing medication combinations. Compared to a medication that operates on a single route, a repurposed medication that interacts with several disease-associated pathways may be more therapeutically relevant. Additionally, within the same disease network, two already available medications may interact with complimentary targets. Therefore, AI may utilise projected drug-target interactions to assess if a combination offers simultaneous regulation of complementary disease processes or wider route coverage. A grading system for choosing lead medication combinations can then incorporate this data.

1.8 AI in advancing pharmaceutical product development

By facilitating data-driven formulation design, optimisation, quality evaluation, and production, artificial intelligence (AI) is progressively revolutionising the creation of pharmaceutical products. AI and machine learning (ML) can analyse large datasets to find relationships between formulation variables, process parameters, and critical quality attributes (CQAs), which reduces development time and experimental effort in contrast to traditional methods that heavily rely on repeated experimental trials (Mak & Pichika, 2019; Paul et al., 2021).

Nanoparticles, liposomes, nanoemulsions, microspheres, solid dispersions, transdermal systems, and controlled-release formulations are just a few of the drug-delivery systems that may be developed using AI. Important features including particle size, encapsulation effectiveness, drug loading, dissolution, drug-release behaviour, and stability may be predicted by ML models, facilitating quick formulation variable optimisation (Vamathevan et al., 2019).

AI also contributes to pharmaceutical manufacturing and quality control by analyzing process and analytical data to detect deviations, optimize manufacturing parameters, and predict product quality. Furthermore, AI-based models can support pharmacokinetic prediction, stability assessment, dosage optimization, and personalized drug-delivery strategies (Paul et al., 2021; Topol, 2019).

Overall, the integration of AI into pharmaceutical product development can improve efficiency, reduce experimental burden, and support the translation of computationally identified drug-repurposing candidates into safe, effective, stable, and manufacturable pharmaceutical products.

1.9 AI in clinical trial design

Artificial intelligence (AI) is increasingly being incorporated into clinical trial design and execution to improve patient selection, trial efficiency, and the prediction of treatment outcomes. Traditional clinical trials are often time-consuming and expensive, with challenges related to patient recruitment, selection of appropriate study populations, trial-site selection, and participant retention. AI and machine learning (ML) can analyze clinical, molecular, and real-world datasets to address several of these limitations (Harrer et al., 2019; Vamathevan et al., 2019).

Patient stratification and selection is a significant use of AI. AI systems can identify individuals who are more likely to satisfy eligibility requirements and react to a certain treatment by analysing demographic, genetic, clinical, and disease-related factors. This can increase the effectiveness of recruiting and make it easier to create more accurate and customised clinical trials (Harrer et al., 2019).

By determining relevant endpoints, assessing recruitment needs, forecasting dropout rates, and choosing optimal trial sites, AI may also aid in the optimisation of clinical trial protocols. In order to improve the design of next trials, machine-learning algorithms can examine past clinical trial data to find variables linked to successful recruitment and trial completion (Vamathevan et al., 2019).

AI can be especially helpful in drug repurposing trials as current medications already have a wealth of pharmacological and safety data. In order to find suitable patient groups and rank prospective repurposing prospects, AI models can use past clinical evidence, real-world data, molecular traits, and disease-specific knowledge. AI may also assist in identifying appropriate patient subgroups and dosage combinations for medication combinations based on anticipated safety and effectiveness.

By evaluating longitudinal clinical data and spotting early signs of treatment response or adverse effects, AI can further help with clinical outcome prediction and patient monitoring. This might assist identify patients who need closer monitoring and allow for adaptive decision-making during clinical development (Harrer et al., 2019).

Overall, AI can improve clinical trial design by supporting patient recruitment, population stratification, protocol optimization, trial-site selection, outcome prediction, and safety monitoring. In the proposed AI-driven drug repurposing framework, these capabilities can facilitate the transition from computationally prioritized lead drug combinations to appropriately designed clinical studies, potentially improving the efficiency and precision of therapeutic development.

1.10 AI in combination drug delivery and synergism/antagonism prediction

Artificial intelligence (AI) is increasingly being applied to combination drug therapy and drug-delivery development, particularly for identifying synergistic drug pairs and predicting potentially antagonistic interactions. Combination therapy can improve therapeutic efficacy by acting on multiple biological targets, reducing drug resistance, and potentially lowering the dose of individual agents. However, the large number of possible drug combinations makes exhaustive experimental screening expensive and time-consuming (Rani et al., 2022; Wang et al., 2024).

To forecast the results of medication combinations, machine learning (ML) and deep learning algorithms can use drug molecular structures, drug-target interactions, gene-expression profiles, disease pathways, pharmacological traits, and prior combination-response data. Neural networks and graph neural networks (GNNs) are examples of advanced techniques that may learn intricate interactions between medications and biological systems, enhancing the discovery of potentially synergistic combinations (Besharatifard & Vafaee, 2024; Wang et al., 2024).

Combinations can be categorised by AI based on their anticipated pharmacological interactions, such as antagonistic, additive, or synergistic. Antagonism happens when the combined impact is less than anticipated, whereas a synergistic combination has a bigger therapeutic benefit than anticipated from the separate medications. Because certain combinations may boost therapeutic activity while others may decrease efficacy or raise the risk of side effects, predicting these interactions is very crucial (Rani et al., 2022; Peng et al., 2024).

By optimising formulation factors and forecasting medication compatibility, release behaviour, stability, and other crucial quality aspects, AI may also help combination drug delivery systems. When two or more repurposed medications are meant to be integrated into

a single delivery system, this is very helpful. The number of necessary experimental trials can be decreased by using AI-based methods to help determine appropriate drug ratios, excipient combinations, release profiles, and formulation conditions. An additional advantage is the integration of clinical and pharmacological data into combination selection. AI-based clinical pharmacy systems can assist in identifying potential drug-drug interactions, optimizing medication therapy, and supporting individualized treatment decisions (Kumari & Kumari, 2026).

For the proposed AI-driven drug repurposing methodology, synergism/antagonism prediction can therefore function as a critical lead-combination selection step. Initially, existing drugs can be ranked according to their predicted activity against disease-associated targets. The shortlisted drugs can then be evaluated in different combinations using AI models incorporating target complementarity, pathway coverage, predicted synergy, antagonistic potential, drug-drug interactions, toxicity, and pharmacological compatibility. The highest-ranked combination can subsequently be selected for experimental validation.

Thus, AI provides a rational bridge between drug repurposing, combination therapy, and pharmaceutical product development, allowing large numbers of possible combinations to be computationally screened before laboratory testing. This approach may improve the probability of identifying effective lead combinations while reducing unnecessary experimental effort.

1.11 Conclusion

Artificial intelligence (AI) is rapidly transforming drug discovery and pharmaceutical research by enabling the integration and analysis of large-scale molecular, pharmacological, clinical, and multi-omics datasets. In particular, AI-driven drug repurposing provides a promising approach for identifying new therapeutic applications of existing drugs while potentially reducing the time, cost, and risks associated with conventional drug development. Machine learning, deep learning, knowledge graphs, network pharmacology, and molecular prediction approaches can facilitate the identification of novel drug-target interactions and disease associations. The integration of AI with personalized medicine, combination drug delivery, pharmacological data, and clinical evidence further strengthens this approach. AI can help identify patient-specific therapeutic opportunities and support the optimization of pharmaceutical products and clinical trial strategies. However, computational predictions should not be considered definitive without appropriate experimental and clinical validation. Data quality, model interpretability, algorithmic bias, generalizability, and regulatory

considerations remain important challenges. Overall, an integrated AI-driven drug repurposing methodology has the potential to provide a systematic pathway from disease characterization and candidate identification to drug-target prediction, combination generation, synergism/antagonism prediction, safety assessment, lead-combination selection, and experimental validation. Continued integration of AI with pharmacology, systems biology, multi-omics, and clinical research may accelerate the discovery of effective and personalized therapeutic combinations and contribute significantly to the future development of precision medicine.

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14. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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