Available online on 15.10.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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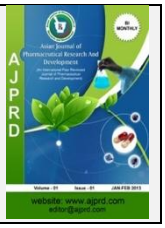

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Review Article

Reimagining Drug Potential: Machine Learning As A Catalyst In Drug Repurposing

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A B S T R A C T

Drug discovery has long been a cornerstone of medical progress, yet the conventional path of developing new therapeutics is notoriously lengthy, costly, and fraught with uncertainty. On average, it requires more than a decade of intensive research, billions of dollars in investment, and multiple phases of preclinical and clinical testing to bring a single novel drug to market. Despite such efforts, the attrition rate remains strikingly high, with only a small fraction of candidates achieving regulatory approval. In this context, drug repurposing, also known as drug repositioning, has emerged as a pragmatic and highly valuable strategy to address unmet medical needs and optimise available therapeutic resources. The history of drug repurposing is deeply embedded in the evolution of modern pharmacology. Early examples demonstrate how serendipitous observations, clinical experiences, and detailed pharmacological studies gave new life to compounds originally designed for unrelated purposes. Aspirin, first introduced as an analgesic and antipyretic, was later recognised for its antiplatelet effects, transforming it into a cornerstone therapy for cardiovascular diseases. Thalidomide, infamous for its teratogenic effects, was subsequently repurposed as an immunomodulatory drug to treat multiple myeloma and leprosy-related complications. Sildenafil, initially developed for angina, gained global recognition when repurposed for erectile dysfunction and later for pulmonary arterial hypertension.

Keywords: Drug Repurposing, Artificial Intelligence, Machine Learning, Drug Discovery, Drug Target Interaction.

A R T I C L E I N F O: Received 11 Feb 2025; Review Complete 05 April 2025; Accepted 18 August 2025. ; Available online 15 Oct. 2025

Cite this article as:
Sanap M P, Jagtap B.T., Reimagining Drug Potential: Machine Learning As A Catalyst In Drug Repurposing, Asian Journal of Pharmaceutical Research and Development. 2025; 13(5):152-160, DOI: http://dx.doi.org/10.22270/ajprd.v13i5.1644

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INTRODUCTION

Drug discovery has long been a cornerstone of medical progress, yet the conventional path of developing new therapeutics is notoriously lengthy, costly, and fraught with uncertainty. On average, it requires more than a decade of intensive research, billions of dollars in investment, and multiple phases of preclinical and clinical testing to bring a single novel drug to market. Despite such efforts, the attrition rate remains strikingly high, with only a small fraction of candidates achieving regulatory approval. In this context, drug repurposing, also known as drug repositioning, has emerged as a pragmatic and highly valuable strategy to address unmet medical needs and optimise available therapeutic resources. The history of drug repurposing is deeply embedded in the evolution of modern pharmacology. Early examples demonstrate how serendipitous observations, clinical experiences, and detailed pharmacological studies gave new life to compounds originally designed for unrelated purposes. Aspirin, first introduced as an analgesic and antipyretic, was later recognised for its antiplatelet effects, transforming it into a

cornerstone therapy for cardiovascular diseases. Thalidomide, infamous for its teratogenic effects, was subsequently repurposed as an immunomodulatory drug to treat multiple myeloma and leprosy-related complications. Sildenafil, initially developed for angina, gained global recognition when repurposed for erectile dysfunction and later for pulmonary arterial hypertension. These milestones illustrate the enduring value of repurposing as both a scientific opportunity and a clinical necessity. What makes drug repurposing particularly attractive is its ability to bypass several hurdles associated with traditional drug discovery. Since the pharmacokinetics, safety profiles, and toxicological data of existing drugs are already well-characterised, the time and cost required to advance them into new therapeutic domains are substantially reduced. Moreover, repurposing minimises the risks of unforeseen adverse effects, thereby offering greater confidence in clinical outcomes. This characteristic not only accelerates patient access to therapies but also provides a sustainable approach for tackling rare, neglected, and emergent diseases where new drug development may not be economically feasible. An equally important aspect lies in the versatility of repurposed drugs. Many approved compounds demonstrate polypharmacology—the ability to interact with multiple molecular targets. This feature allows them to be repositioned across diverse therapeutic areas, ranging from oncology and infectious diseases to neurological and autoimmune disorders. Furthermore, the repurposing paradigm aligns well with the principles of precision medicine, as drugs can be matched with specific patient populations based on their molecular or physiological characteristics. The ideal characteristics of a drug suitable for repurposing extend beyond established safety and pharmacokinetics. A strong candidate typically possesses well-documented mechanisms of action, broad-spectrum biological activity, and a favourable therapeutic index. Additionally, compounds with structural diversity or known interactions with multiple signalling pathways tend to have higher repurposing potential. Drugs with extensive post-marketing surveillance data also offer valuable insights into long-term tolerability, further strengthening their candidacy for repositioning. The relevance of drug repurposing has been repeatedly validated during times of medical urgency. The global health crisis brought on by the COVID-19 pandemic highlighted its value once again, as researchers rapidly turned to existing pharmacological libraries to identify possible antiviral and supportive treatments. This unprecedented situation underscored the adaptability and resilience of the repurposing framework in addressing urgent therapeutic gaps under pressing timeline.

Importance of Machine Learning in Drug Repurposing

Drug discovery has been a complex, costly, and time-intensive process that requires an average of 10–15 years and billions of dollars before a new molecule reaches the market [1]. Traditional approaches had focused on de novo drug design, but the high attrition rates during preclinical and clinical phases had hindered success [2]. In this context, drug repurposing has emerged as a strategic alternative that leverages the existing safety profiles of approved drugs for novel therapeutic uses, thereby reducing costs and development timelines [3]. Machine learning (ML) tools have gained significance in drug repurposing because they have allowed the rapid integration and analysis of high-dimensional biomedical data, including genomics, proteomics, transcriptomics, and clinical records [4]. These computational methods had enhanced the prediction of drug–target interactions, disease–gene associations, and phenotype similarities, which had been crucial for identifying new therapeutic indications of old drugs [5]. The importance of ML-based drug repurposing had been highlighted during global health emergencies, such as the COVID-19 pandemic, where computational pipelines had accelerated the identification of repurposed candidates like remdesivir, hydroxychloroquine, and baricitinib [6]. Beyond pandemics, ML has been applied to chronic and rare diseases, providing hope for patients where traditional R&D pipelines have not delivered [7]. Thus, the incorporation of ML in drug repurposing had not only promised cost-efficiency but had also advanced precision medicine strategies by aligning therapies with patient-specific molecular signatures [8].

Conventional Methods of Machine Learning in Drug Repurposing

Early ML applications in drug repurposing had relied on supervised, unsupervised, and semi-supervised learning approaches that had processed structured biomedical data [9]. Supervised learning methods such as support vector machines (SVM), random forests (RF), and logistic regression have been used to classify drug–disease relationships based on labelled training datasets [10]. These models had predicted whether a drug could be repurposed for a specific disease by learning from known positive and negative associations [11]. Unsupervised learning approaches, such as clustering and dimensionality reduction, had been employed when labelled data had been limited. Clustering algorithms like k-means and hierarchical clustering had grouped drugs based on similarity in chemical structures, transcriptomic responses, or adverse effect profiles, thereby uncovering potential shared therapeutic targets [12]. Principal component analysis (PCA) and t-distributed stochastic neighbour embedding (t-SNE) had facilitated visualisation of drug–disease interaction networks in reduced dimensions [13]. Semi-supervised learning had been advantageous because it had combined small labelled datasets with large unlabelled biomedical repositories. For instance, graph-based semi-supervised models had integrated heterogeneous data sources such as drug–target interactions, protein–protein interaction

networks, and disease ontologies to infer novel drug–disease links [14]. Another conventional ML strategy had involved similarity-based prediction, where chemical structure similarity, side-effect similarity, and gene-expression similarity had been used to match drugs to new indications. For example, Campillo et al. (2008) [15] had demonstrated that drugs with overlapping side-effect profiles often shared molecular targets, which had provided a basis for repositioning. Connectivity Map (CMap) analyses had matched disease gene-expression signatures with drug-induced transcriptional responses to identify therapeutic reversals [16]. Furthermore, ensemble learning techniques have been widely employed in conventional repurposing studies. Random forests and gradient boosting methods had aggregated predictions from multiple weak learners to improve accuracy in identifying candidate drugs [17]. These approaches had proven beneficial in high-throughput screening datasets, where noise and variability had posed challenges to single-model predictions. Despite their promise, conventional ML methods had faced limitations. They had depended heavily on feature engineering, requiring domain expertise to select relevant molecular descriptors, pathway features, or pharmacological parameters [18]. Moreover, these methods had struggled with scalability when applied to modern big data sources such as single-cell transcriptomics or electronic health records [19].

Drug repurposing had not been a novel concept; several drugs had already been repositioned successfully for new indications even before machine learning tools had been widely adopted [20]. These cases have illustrated the feasibility and practicality of repositioning strategies in pharmaceutical research.

Examples of Drugs Which Had Been Reused Before for Other Diseases:

1. Sildenafil (Viagra®: Sildenafil had originally been developed by Pfizer as an anti-hypertensive and anti-anginal agent, targeting phosphodiesterase type 5 (PDE5) [21]. During clinical trials, it had failed to show sufficient efficacy in angina but had demonstrated a remarkable effect in treating erectile dysfunction [22]. This serendipitous observation had led to its repositioning and eventual blockbuster success. Later, sildenafil had also been approved for pulmonary arterial hypertension, further proving its repurposing potential [23].

2. Thalidomide: Thalidomide had been withdrawn in the 1960s due to teratogenic effects when it had been prescribed for morning sickness in pregnant women [24]. However, decades later, researchers had discovered its immunomodulatory and anti-angiogenic properties [25]. This had paved the way for its repurposing in the treatment of multiple myeloma and leprosy-associated erythema nodosum leprosum.

3. Minoxidil: Minoxidil had initially been developed as an oral antihypertensive agent due to its vasodilatory effect [26]. During clinical use, patients had been observed to experience hypertrichosis (excessive hair growth) as a side effect. This had ultimately led to its topical reformulation and approval for androgenic alopecia treatment [27].

4. Zidovudine (AZT): Zidovudine had first been synthesised in 1964 as a potential anti-cancer drug but had failed in oncology [28]. In the 1980s, it had been repurposed as the first approved antiretroviral drug for HIV/AIDS after it had shown potent inhibition of reverse transcriptase [29].

5. Methotrexate: Methotrexate was originally designed as a chemotherapeutic agent targeting rapidly dividing cancer cells [30]. Later, its immunosuppressive properties had been recognised, and it had been repurposed for the treatment of autoimmune conditions such as rheumatoid arthritis and psoriasis [31].

6. Aspirin: Aspirin (acetylsalicylic acid) was first developed as an analgesic and anti-inflammatory drug [32]. Over time, it had been repurposed for cardiovascular disease prevention due to its antiplatelet activity, which had reduced the risk of myocardial infarction and stroke [33].

7. Remdesivir: Originally developed for Ebola virus disease, remdesivir was later repurposed as one of the first antiviral drugs authorised for emergency use against COVID-19 [34]. Although its efficacy had been debated, its rapid repositioning had underscored the importance of computational drug repurposing during pandemics.

8. Baricitinib: Baricitinib, a Janus kinase (JAK) inhibitor used for rheumatoid arthritis, had been identified through AI-driven repurposing pipelines as a potential treatment for COVID-19 due to its dual antiviral and anti-inflammatory properties [35]. The drug had subsequently received emergency approval.

Innovative Applications of Machine Learning in Drug

1. Network-based Approaches: One of the most innovative applications of ML in drug repurposing has been the development of network-based methods. Biological systems had been represented as interconnected networks of proteins, genes, metabolites, and diseases [36]. Machine learning algorithms had been applied to analyse these complex networks to identify potential repurposing opportunities. For instance, drug–disease bipartite networks, drug–target interaction networks, and disease–gene association graphs had been constructed to identify hidden therapeutic links [37]. Graph neural networks

(GNNs) have further advanced this area by learning node embeddings that capture topological and biological similarity across networks [38].

2. Deep Learning Applications: Deep learning has represented a paradigm shift in repurposing strategies. Convolutional neural networks (CNNs) had been used to predict drug–target binding by learning from structural and chemical features [39]. Recurrent neural networks (RNNs) have been employed to model sequential biological data such as protein amino acid sequences or drug SMILES strings [40]. Autoencoders had been applied to reduce dimensionality and extract meaningful latent representations from large-scale omics datasets, enabling the discovery of repurposable drug candidates [41]. Generative adversarial networks (GANs) had also been utilised to simulate novel drug–disease associations by generating synthetic but biologically plausible data points that had complemented limited real-world datasets [42]. These methods had enhanced the ability to generalise predictions across diverse therapeutic areas.

3. Multi-Omics Integration: An innovative frontier in ML-driven repurposing has been the integration of multi-omics data. Transcriptomic, proteomic, metabolomic, and epigenomic datasets had been combined to provide holistic views of disease mechanisms and drug responses [43]. ML algorithms such as multi-kernel learning and ensemble frameworks have been applied to harmonise diverse data modalities. For example, integrating transcriptomic profiles with drug-induced perturbation signatures has enabled the identification of repurposing candidates for neurodegenerative diseases [11].

4. Real-World Evidence (RWE) Mining: Electronic health records (EHRs), insurance claims, and patient registries have offered real-world evidence that has been mined using machine learning for repurposing purposes. Natural language processing (NLP) algorithms had extracted drug–disease relationships from unstructured clinical notes [44]. For instance, retrospective EHR analysis had suggested the antidiabetic drug metformin as a potential anti-cancer candidate by identifying lower cancer incidence among diabetic patients treated with metformin [45]. ML-enhanced RWE analysis had therefore uncovered repositioning opportunities that had been less apparent in controlled experimental datasets.

5. Drug Combination Repurposing: Innovative ML applications have also explored drug combinations, where two or more existing drugs have been identified to act synergistically for new indications. Machine learning methods such as matrix factorisation and deep reinforcement learning have been used to predict synergistic effects of drug pairs [46]. This had been particularly relevant in oncology and infectious diseases, where combination therapy had been standard practice.

6. Patient-Specific Repurposing: Personalised or precision medicine approaches have also benefited from innovative ML applications. Algorithms had stratified patients based on genetic or phenotypic profiles to identify subgroups that had been more likely to respond to a repurposed drug [47]. For example, ML-driven transcriptomic analysis had suggested that certain cancer patients with specific gene-expression signatures could benefit from drugs repurposed from unrelated therapeutic areas [48].

7. Pandemic Preparedness and Rapid Response: During the COVID-19 pandemic, innovative machine learning pipelines had been deployed to screen massive drug libraries against viral targets in weeks, compared to years in traditional pipelines [4]. Platforms integrating molecular docking, transcriptomics reversal signatures, and AI-driven prioritisation had identified candidates like baricitinib, dexamethasone, and tocilizumab [35]. These innovative approaches have demonstrated the critical role of ML in accelerating emergency therapeutic discovery.

Application of Artificial Intelligence in Drug Repurposing:

1. AI-powered Literature and Knowledge Mining: The biomedical literature contains a massive amount of unstructured text data, including clinical trial outcomes, drug safety reports, and mechanistic studies. AI-driven natural language processing (NLP) tools had extracted drug–disease associations from millions of publications, patents, and clinical records [34]. Systems like IBM Watson had been applied to mine text-based biomedical databases, thereby generating hypotheses for drug repurposing at a scale that manual curation could not achieve [50]. These AI-driven pipelines had reduced the time needed to identify candidate repositioning opportunities.

2. Reinforcement Learning in Repurposing: Reinforcement learning (RL), an AI paradigm where agents have been trained to make sequential decisions by maximising rewards, has been applied to drug repurposing scenarios [46]. RL agents had explored chemical space or disease–drug interaction networks to iteratively identify drug candidates that maximised therapeutic relevance while minimising adverse effects. Such approaches had been particularly valuable in repurposing drug combinations, where the synergy between multiple agents had been optimised through trial-and-error learning in silico.

3. AI for Rare and Neglected Diseases: One of the most impactful applications of AI in repurposing has been for rare and neglected diseases, where traditional drug

discovery investments had been limited due to low market incentives [3]. AI-based algorithms have enabled the identification of cost-effective repositioning candidates by matching existing drugs to rare disease pathophysiology using genomic and clinical data [58]. For instance, AI tools had suggested the repositioning of the cancer drug nilotinib for neurodegenerative disorders such as Parkinson's disease based on its ability to modulate autophagy pathways [59].

4. AI in Pandemic Preparedness and Infectious Diseases: AI applications have played a particularly prominent role in pandemic preparedness. During the COVID-19 pandemic, AI had been used to screen existing antivirals, immunomodulators, and anti-inflammatory drugs against SARS-CoV-2 targets within weeks [13]. AI-driven models such as Benevolent AI's knowledge graph approach had identified baricitinib as a candidate for COVID-19, leading to its emergency authorisation [35]. Similarly, AI platforms had suggested potential repurposing of drugs like lopinavir–ritonavir and tocilizumab during the early outbreak phase [8].

5. AI-driven Polypharmacology and Side-effect Profiling: Polypharmacology, where a drug interacts with multiple targets, has often been the basis for successful repurposing. AI models had been developed to predict secondary pharmacological effects of drugs, thus uncovering opportunities for repositioning [60]. Likewise, AI had been employed to analyse adverse event databases to detect signals of unexpected therapeutic benefits. For instance, EHR mining with AI had suggested metformin's protective effects against certain cancers [45].

Advantages of Machine Learning and AI in Drug Repurposing:

The integration of machine learning (ML) and artificial intelligence (AI) into drug repurposing pipelines has offered several advantages that traditional methodologies have not been able to achieve. These advantages have ranged from reduced development costs and timelines to enhanced prediction accuracy, improved scalability, and better patient stratification [5].

1. Reduction in Cost and Time: One of the most significant advantages has been the drastic reduction in both cost and time required for drug discovery. Traditional de novo drug development had taken over a decade and had required billions of dollars in investment [2]. By contrast, ML- and AI-driven repurposing had leveraged existing drugs with known safety profiles, which had significantly shortened preclinical phases and reduced overall costs [3]. For example, during the COVID-19 pandemic, AI-based tools had identified baricitinib as a candidate treatment within weeks, whereas conventional drug discovery would have taken years [35].

2. Improved Prediction Accuracy: AI models have demonstrated superior accuracy in predicting drug–target interactions and disease associations compared to conventional statistical methods. Deep learning algorithms, graph neural networks, and ensemble models had captured complex, nonlinear biological patterns that traditional models had missed [38]. This improvement in accuracy has increased the likelihood of successful repurposing outcomes, reducing attrition rates in clinical trials.

3. Scalability for Big Data Integration: Another advantage was scalability. Modern biomedical research has generated massive datasets, including genomics, proteomics, metabolomics, and real-world clinical data. Traditional methods had struggled to integrate such high-dimensional datasets, whereas ML and AI had handled them efficiently [43]. By combining multi-omics and clinical records, AI-driven models have enabled holistic repurposing predictions across diverse diseases.

4. Discovery of Hidden Patterns and Relationships: AI algorithms have excelled in uncovering hidden relationships within data that had not been apparent through conventional analysis. For instance, NLP-based AI models had mined unstructured biomedical literature to detect novel drug–disease links, while graph-based models had revealed indirect therapeutic associations in biological networks [44]. This ability had broadened the spectrum of repositioning opportunities across therapeutic areas.

5. Patient Stratification and Precision Medicine: Another key advantage has been the contribution to personalised medicine. ML and AI tools had stratified patients based on genetic, transcriptomic, or clinical features, thereby predicting which subgroups had been most likely to benefit from repurposed drugs [48]. This precision-driven approach has improved treatment outcomes while minimising adverse effects, aligning drug repurposing with the goals of precision medicine.

6. Facilitation of Drug Combination Repurposing: AI had also facilitated the identification of effective drug combinations, a task that had been computationally intensive with traditional methods. Deep reinforcement learning and matrix factorisation approaches had predicted synergistic drug interactions more accurately, accelerating the discovery of novel combination therapies for oncology, infectious diseases, and neurodegenerative disorders [46].

7. Real-world Validation and Evidence-based Insights: AI-driven analysis of electronic health records, insurance claims, and adverse event reporting systems has provided real-world validation of repurposing hypotheses. This had been a critical advantage because real-world data had often reflected treatment responses across diverse populations outside controlled clinical trial settings [45]. Such validation had improved the translational potential of repurposed andidates.

Challenges in Machine Learning and AI-driven Drug

1. Data Availability and Quality: One of the primary challenges had been the dependence on large, high-quality datasets. Although biomedical research had produced vast amounts of data, much of it had been incomplete, heterogeneous, or noisy [19]. For example, gene-expression datasets had often contained batch effects, while electronic health records had suffered from missing values and inconsistent reporting [51]. Such limitations had reduced the reliability of ML predictions.

2. Data Integration Across Modalities: Another challenge had been the integration of multi-modal data sources, including genomics, proteomics, metabolomics, and clinical outcomes. While AI had been able to process diverse datasets, harmonising them across different platforms, populations, and formats had remained difficult [43]. Lack of standardised ontologies and interoperable formats had further complicated the creation of unified databases for repurposing studies.

3. Interpretability of AI Models: AI-driven models, particularly deep learning networks, have often been criticised as “black boxes” because their decision-making processes have not been easily interpretable [52]. In drug repurposing, the lack of interpretability has been a major concern because regulatory agencies and clinicians have required mechanistic explanations before approving or adopting repurposed therapies. Without interpretability, AI predictions had struggled to gain clinical trust.

4. Bias and Generalizability AI models had been prone to biases if training data had been skewed toward certain populations, diseases, or drug classes. For instance, models trained primarily on Western population data had not always generalised well to Asian or African cohorts [53]. Similarly, drug–disease association models had sometimes been biased toward well-studied drugs, leaving rare diseases underrepresented. These biases had limited the equity and universality of repurposing predictions.

5. Validation Gap Between Prediction and Clinic: A significant challenge has been the gap between computational predictions and clinical validation. While ML pipelines had identified thousands of potential repurposing candidates, only a fraction had advanced to clinical trials, and even fewer had achieved regulatory approval [3]. This gap had been due to the high cost and time required for experimental and clinical validation, which had remained a bottleneck.

6. Improved Data Infrastructure: Future progress had depended on the development of standardised, interoperable, and high-quality biomedical databases. Initiatives to harmonise omics data, clinical trial results, and real-world evidence had been crucial for ensuring reliable repurposing predictions [43].

7. Explainable AI Models: Advances in explainable AI (XAI) had been expected to improve the interpretability of predictions, making computational insights more acceptable to clinicians and regulatory agencies [52]. By providing mechanistic reasoning alongside predictions, XAI had been projected to build trust in AI-driven pipelines.

8. Integration with Digital Health and Wearables: The incorporation of real-time patient data from wearable devices and digital health platforms has been seen as a powerful addition to drug repurposing. AI models had been anticipated to use continuous patient monitoring data to refine and personalise repurposing predictions [49]

9. Advances in Synthetic Biology and Systems Pharmacology: ML had been projected to integrate more deeply with synthetic biology and systems pharmacology, enabling in silico modelling of drug–disease–host interactions and predicting repurposing outcomes at a systems level [36].

10. Global Collaborations and Open Science: Large-scale, global collaborations have been essential for sharing data, computational resources, and expertise. Open-access repurposing platforms had been predicted to democratize drug discovery and ensure that repurposing strategies benefited not only profitable indications but also rare and neglected diseases [3].

11. Regulatory Adaptations: Regulatory bodies had been expected to evolve frameworks to accommodate AI-driven drug repurposing by setting guidelines for validation, reproducibility, and transparency [54]. Policies encouraging repurposing investment despite weak intellectual property protection had also been anticipated.

12. Integration of Quantum Computing: In the longer term, the rise of quantum computing has been foreseen to accelerate AI-driven molecular simulations and drug–target interaction predictions, thereby further advancing repurposing pipelines.

13. Future Scope:

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CONCLUSION

1. Machine learning and artificial intelligence have already transformed drug repurposing into a faster, more cost-effective, and more precise approach compared to traditional methods. The future had promised even greater integration of computational models with experimental and clinical pipelines, ultimately delivering more accessible, effective, and personalised therapies for patients worldwide. By overcoming existing challenges and fostering collaborative innovation, ML and AI have been positioned to become indispensable pillars of 21st-century pharmaceutical research

2. The authors would like to express their heartfelt gratitude to their respected guides and mentors for their invaluable support, encouragement, and constructive feedback throughout the preparation of this review. We sincerely thank our institution for providing access to resources and literature that greatly facilitated this work. Our appreciation also goes to all researchers whose studies have been cited, as their contributions form the backbone of this review. Lastly, we are deeply grateful to our family and friends for their constant motivation and encouragement.

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