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AI for Drug Discovery: From Algorithms to Medicines

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A B S T R A C T

The growing integration of artificial intelligence with molecular dynamics simulations has introduced new possibilities for fostering and improving the discovery of inhibitors in drug development. This study aimed to systematically review how AI fosters MD. The researcher has focused on the methodological applications, reported benefits as compared with classical approaches, therapeutic contexts, and existing gaps. A structured review of peer-reviewed literature showed that AI has been integrated across various important domains. These integrations consistently improved accuracy, computational efficiency, and decision-making value. However, its applications span across kinases, viral proteins, and GPCRs. Although viral proteins and GPCRs have shown more mature applications, kinase-focused research appears comparatively limited. Despite these advances, notable challenges also persist, which include methodological opacity, lack of standardized benchmarks, and limited translational validation. The findings suggest that AI does not replace MD as it serves as a complementary approach that strengthens predictive and interpretive capacity. Thus, this review emphasizes the importance of standardized datasets, reproducible workflows, and experimental translation for maximizing the impact of AI-MD frameworks in drug discovery.

Keywords: Artificial intelligence, Molecular dynamics, Drug discovery, Machine learning, Kinases, GPCRs, Viral proteins.

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INTRODUCTION

Background: Challenges in traditional drug discovery

Drug discovery is a risky and costly process that takes a long time and necessitates efficient decision-making due to the high failure rates and time-consuming process (Wouters et al., 2020). Recent studies put the approximate costs of total R&D that produce a medicine approved for market at between $380.0 to $418.0 billion, which is associated with significant uncertainty and a high risk of financial loss (Sertkaya et al., 2024). Of the programmes initiated in 2011-2020, very few were approved, which highlights the high attrition rates during the phases (Biotechnology Innovation Organization, 2020). Early discovery also must explore huge chemical and conformational space; libraries of structures that can be readily synthesized have grown to tens of billions of structures, which is many times greater than can be experimentally tested (Carlsson and Luttens, 2024; Korn et al., 2023). The flexibility of proteins and structured water is difficult to model with fixed systems, and adds to the uncertainty in affinity and selectivity, which are

involved in binding (Ahmed et al., 2023; Szalai et al., 2024).

Role of Computer-Aided Drug Discovery and limitations of classical Molecular Dynamics

Computer-Aided Drug Discovery (CADD), spanning docking, pharmacophores, QSAR, and related approaches, helps narrow search spaces and prioritise synthesis by learning structure-activity patterns and proposing plausible binding modes (Ahmed et al., 2023; Oselusi et al., 2024). Molecular Dynamics (MD) adds atomistic realism by simulating protein–ligand systems in explicit solvent, revealing induced fit, metastable states, and solvent effects that influence recognition and binding (Ahmed et al., 2023; Patil et al., 2024; Salo-Ahen et al., 2020). However, classical MD faces persistent limits: insufficient sampling of rare events on microsecond-millisecond timescales, force-field inaccuracies, and difficulties assessing convergence for reliable thermodynamics (Bastida et al., 2024; Hénin et al., 2022; Wang et al., 2024). Enhanced-sampling methods mitigate but do not remove the timescale burden, and they add methodological complexity to already demanding workflows (Mehdi et al., 2024; Shen et al., 2023). Even with best practices, free-energy pipelines require careful system setup and substantial computing, which constrains throughput in live projects (Salo-Ahen et al., 2020; York, 2023).

Emergence of Artificial Intelligence

Recent advances in machine learning provide new ways to represent molecules and proteins and to learn from structural and biophysical data at scale (Visan and Negut, 2024). Supervised models and graph neural networks improve property prediction and prioritisation, while transformers and geometric deep learning capture long-range and 3D relationships relevant to binding (Abbas et al., 2024; Obaido et al., 2024; Qureshi et al., 2023). Diffusion models now produce poses and complexes that outperform many traditional search-based docking methods under benchmark conditions, enabling faster screening with calibrated confidence estimates (Corso et al., 2022; Nakata et al., 2023). Artificial Intelligence (AI) also accelerates or augments MD by guiding sampling, learning collective variables, or supplying surrogates and learned force fields that retain accuracy while reducing cost (Galvelis et al., 2023; Mehdi et al., 2024; Röcken and Zavadlav, 2024).

Artificial intelligence has transformed how molecular information is represented, predicted, and generated (Joshi and Kumar, 2021; Karthikeyan and Priyakumar, 2022). Transformers model sequences and 3D relationships, enabling long-range context for affinity and selectivity (Huang et al., 2023; Jiang et al., 2025). Diffusion models map distributions over structures and molecules, supporting controllable design (Wang et al., 2025). At the same time, specialized hardware and software have lowered the barrier to training and inference. When combined with molecular dynamics, AI capabilities open new workflows. Learned bias potentials and adaptive sampling can focus trajectories on relevant states. Machine-learned force fields and hybrid quantum-classical models can improve accuracy while preserving speed (Couzinié et al., 2025; Willow et al., 2025). Surrogate models can stand in for costly steps, enabling wider exploration under fixed budgets. Together, AI and MD promise a balance of physical realism and computational efficiency, with the potential to meaningfully shorten cycles, increase confidence before synthesis, and expand the accessible chemical spaces. New datasets that pair trajectories with binding labels (for example, protein-ligand MD traces) further support training and benchmarking of AI-MD hybrids (Siebenmorgen et al., 2024). In parallel, deep generative models and diffusion-based energy landscapes can suggest states for MD to refine, improving the balance between exploration and physical validation (Lu et al., 2024).

Evidence on AI-augmented MD is growing quickly but remains fragmented across chemistry, machine learning, and structural biology outlets, making it difficult to compare methods and judge when they outperform classical baselines. Reporting practices vary widely: many studies differ in dataset curation, split strategies, baseline selection, uncertainty reporting, and convergence checks, which complicates fair assessment and reproducibility (Heil et al., 2021). To support robust evaluation of AI-MD methods and their translational potential, recent community guidance emphasises transparent documentation of data, code, models, and computational environments (Kapoor et al., 2024). The broader FAIR (Findable, Accessible, Interoperable, and Reusable) movement also encourages practices that make data and software findable, accessible, interoperable, and reusable across teams, which is directly relevant to AI-MD pipelines (Welter et al., 2023; Whitacre et al., 2024). Given these dynamics, a structured and transparent review can map integration patterns, summarise benefits and limits, and highlight open problems where consensus and better evidence are needed (Visan and Negut, 2024).

The main aim of this study is to systematically evaluate how artificial intelligence integrates with molecular dynamics to improve inhibitor discovery, focusing on kinases, viral proteins, and GPCRs, by synthesising evidence from the last

decade across 20 peer-reviewed studies.

This review pursues four objectives: catalogue AI-MD integration patterns, evaluate performance and efficiency against established baselines, situate applications by therapeutic area, and surface methodological gaps that limit reproducibility and adoption. Against these objectives, the review asks four questions in direct alignment with the study idea:

1. What AI methods have been applied to enhance MD simulations in drug discovery?
2. What are the reported benefits and limitations of AI-driven MD approaches compared to classical methods?
3. What therapeutic areas have seen successful applications of AI-augmented MD?
4. What gaps and challenges remain for future research?

MATERIALS AND METHODS

This review applies a transparent and reproducible approach to identify, appraise, and synthesise research on artificial intelligence augmented molecular dynamics (AI-MD) for drug discovery. Reporting follows PRISMA 2020 so that search steps, screening decisions, and inclusion counts are traceable end-to-end (Page et al., 2021).

Focus and Justification

The review concentrates on studies where AI is used together with MD to identify or optimise small-molecule inhibitors for kinases, viral proteins, or GPCRs because these target classes are central in modern discovery and have recent, high-quality evidence bases. Kinases remain a major drug class with dozens of approvals, which makes them a strong testbed for methods that aim to improve efficiency and accuracy (Roskoski Jr, 2024). GPCRs account for a large share of approved drugs and continue to benefit from structure-based campaigns, so improvements at the AI-MD interface are directly relevant to translation (Zhang et al., 2024). Viral proteins (for example, viral proteases) are validated therapeutic targets in antiviral discovery, providing clear biochemical readouts for benchmarking AI-MD pipelines (Borges et al., 2024). The time window is the last ten years to capture the deep-learning era and the rapid growth of ML-enhanced sampling and learned potentials that make AI-MD integration feasible in practice. The final sample is twenty peer-reviewed articles, which enables depth of extraction across methods and targets while preserving breadth across the three therapeutic areas.

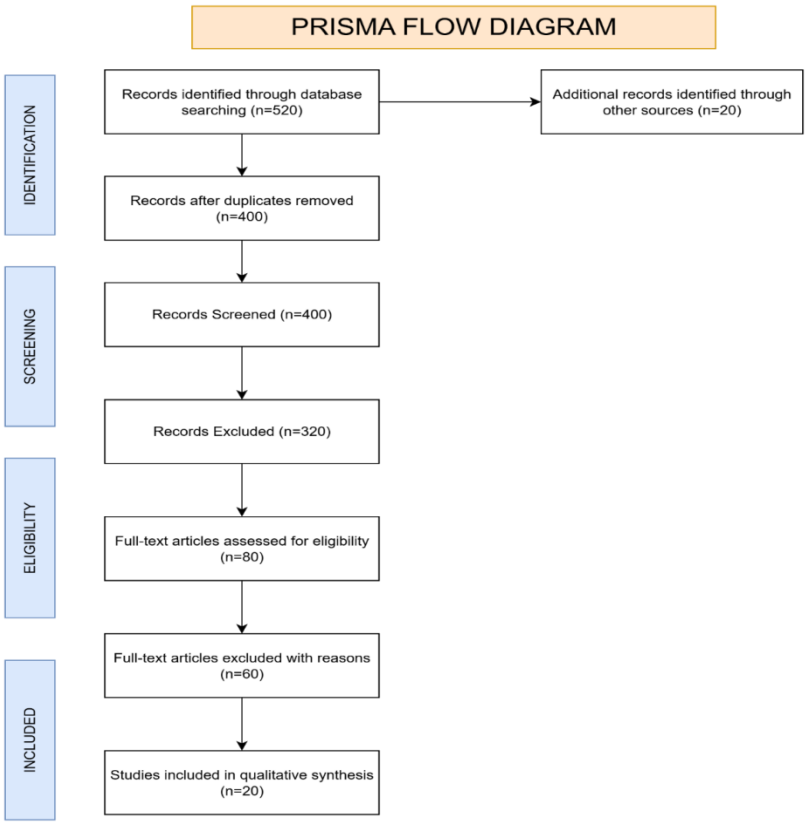

Figure 1: PRISMA Flow Diagram (Source: Author-generated).

Eligibility Criteria

Eligible records are original studies that: (a) combine an AI or machine-learning component with MD in a single workflow; (b) address a drug-discovery task relevant to inhibitor identification, pose refinement, free-energy estimation, or prioritisation; (c) report at least one evaluable outcome (for example, affinity error, pose RMSD, enrichment, hit rate, or compute/time); (d) involve kinases, viral proteins, or GPCRs; and (e) are published in English within the last ten years. Reviews, editorials, AI-only or MD-only studies, purely materials-science simulations, and records without measurable outcomes are excluded.

Information Sources and Search Strategy

Searches cover PubMed/MEDLINE, Scopus, Web of Science Core Collection, IEEE Xplore, and ACM Digital Library. The core Boolean string combines AI terms ("machine learning," "deep learning," "graph neural network," "transformer," "diffusion") with MD terms ("molecular dynamics," "enhanced sampling," "free energy," "force field") and drug-discovery terms ("protein-ligand," "docking," "inhibitor," "kinase," "GPCR," "viral protease").

Screening and Selection

All records are exported and deduplicated. Title/abstract screening and full-text review are performed independently by two reviewers using a piloted form; disagreements are resolved by discussion. Reasons for exclusion are recorded in the full text to ensure auditability under PRISMA 2020. The target is twenty papers that meet all criteria and collectively cover the three therapeutic areas and the main AI-MD integration modes.

Data Extraction

A standardised template captures: bibliographic details; target class and biological system; AI approach (for example, graph neural networks, transformers, diffusion or other generative models); MD details (engine, force field, solvent/ions, timescale, any enhanced sampling); datasets and benchmarks; baselines; outcomes with units; uncertainty reporting; compute cost or speedup; code and data availability; and authors' stated limitations. Extraction is piloted on three papers and then performed in duplicate. The template emphasises items needed to judge whether AI improves sampling efficiency, accuracy, or decision value over established MD and docking baselines.

Quality Appraisal and Reproducibility

Risk of bias is assessed with a checklist adapted for ML-based science, covering dataset integrity and leakage avoidance, clarity of train/validation/test splits and any external validation, adequacy and fairness of baselines, transparency of model selection and hyper-parameters, statistical uncertainty (replicates, confidence intervals), MD protocol completeness and convergence checks, and reproducibility (code/data/environment availability).

Synthesis Plan

A narrative synthesis organises findings by AI-MD integration role and by therapeutic area, with tables that compare outcomes and compute cost against classical baselines. Where studies report compatible metrics on similar tasks and datasets, random-effects meta-analysis may be attempted; otherwise, effect-direction summaries are used. The synthesis explicitly distinguishes peer-reviewed evidence from preprints, and comments on the readiness level of each approach for kinase, viral, or GPCR programmes.

Transparency

The full search strings, inclusion decisions, extraction forms, and synthesis code will be shared as supplementary material to support reuse and replication, reflecting current recommendations for open and reproducible ML-enabled science (Kapoor et al., 2024).

RESULTS

Results Orientation and Mapping to Research Questions

This Results section reports findings from 20 peer-reviewed studies on AI-augmented molecular dynamics within a PRISMA-aligned review framework (Page et al., 2021). Themes were derived through manual, RQ-guided coding; findings are organized by research questions with cross-references to kinases, viral proteins, and GPCRs.

Corpus Description: Studies, Years, Venues, Designs

The corpus comprises 20 peer-reviewed studies published between 2018 and 2025, all within the ten-year eligibility window specified in the protocol. All records are journal articles; no conference papers were identified in the extraction. Designs are predominantly computational, with three studies reporting computational analyses alongside experimental or assay-level follow-up; no explicit statements of external validation on an independent test set were identified in the extraction notes. Therapeutic coverage is largely general-method: eighteen papers present cross-target or platform-level approaches, one focuses on viral proteins, and one on GPCRs; no kinase-specific study appears as a dedicated subset in this corpus. Outcome reporting is mainly conceptual or qualitative; several studies describe performance in terms of model discrimination or prioritization.

Coding and Thematic Procedure (Manual, RQ-Guided)

Thematic analysis was conducted manually: each study was coded against the four research questions, and codes were

iteratively consolidated into higher-order themes (RQ1 integration modes; RQ2 benefits/limitations; RQ3 therapeutic applications; RQ4 gaps), following contemporary reflexive thematic analysis guidance (Braun and Clarke, 2023). Exemplar quotations and metrics were extracted verbatim, when available, to ground themes in evidence.

RQ1 – What AI methods have been applied to enhance MD?

Theme A: Guided/Enhanced Sampling

This theme covers methods where artificial intelligence guides exploration of conformational space by learning collective variables, proposing adaptive sampling policies, or steering simulations toward rare but relevant transitions. The use of artificial intelligence (AI) in drug discovery has introduced a new era of innovation and efficiency in precision medicine (Nayarisseri et al., 2021; Raparthi et al., 2022; Tiwari et al., 2023). Besides MD simulations, other methods of computation exist, but they can broadly be described as machine-learning-based methods, which need to be trained on experimental data (Salo-Ahen et al., 2020). The typical workflow first trains an AI model on preliminary trajectories or structural ensembles, proposes states or reaction coordinates, and then runs molecular dynamics focused on those regions; evaluations report whether trajectories visit more diverse states and whether target events occur sooner, alongside convergence checks where available (Mehdi et al., 2024; Prašnikar et al., 2024; Sarkar et al., 2023). Practically, in the use of ML, the workflow is usually fixed (Kaptan and Vattulainen, 2022). A large number of software packages used to do MD of biomolecules exist, including GROMACS, AMBER, NAMD, OpenMM and CHARMM (Cui et al., 2025; Salo-Ahen et al., 2020), indicating the prevalence of community tooling of enhanced sampling. In recent years, AI usage rose in drug discovery (Agrawal, 2018), and structural biology has shown numerous clinically relevant 3D protein structures. The most prominent of these breakthroughs is in G protein-coupled receptors (GPCRs), ion channels, and other membrane proteins- more than half of drug targets- that have offered potent ligand screening and lead optimization opportunities (Wei and McCammon, 2024).

Theme B: Learned Force Fields / ML Potentials

Machine learning (ML) has been used in all types of problems in biomolecular simulations. It assists in turning out significant structural features to analyze and enhances the signal-to-noise ratio by eliminating redundant degrees of freedom within the system or the process under investigation (Kaptan and Vattulainen, 2022). Recent work trains graph-based or neural potentials on large quantum-chemical datasets and deploys them in protein-ligand systems, reporting higher fidelity to reference energies and competitive binding-relevant accuracy (Sun et al., 2022). The reference data to be used in the training process of any machine learning (ML) model should be split into two distinct subsets: training/validation and testing. A training/validation set is employed to fit and refine the model, whereas only the test set is employed after the training to assess the generalization performance, i.e., the performance of the model on unknown data (Unke et al., 2021). Reported constraints include domain limits of the training data, treatment of long-range interactions, and handling of polarization and charged groups, which remain active areas of development (Salo-Ahen et al., 2020; Sun et al., 2022; Unke et al., 2021). Emerging toolchains (for example, OpenMM plugins for deep potentials) have lowered barriers to testing ML potentials within existing workflows. For instance, a study reported that quantum mechanical molecular dynamics (QM-MD) can be used to model electronic polarization and is computationally expensive and limited to reasonably small numbers of atoms. In comparison, more powerful and more efficient molecular dynamics simulations can be conducted due to the high computational power and parallel processing of the graphical processing units (GPU) (Fullenkamp et al., 2025; Qureshi et al., 2023).

Theme C: Scoring, Refinement, and Free-Energy Correction

AI models are used to re-score docking poses, refine geometries before or after short MD, and correct free-energy estimates to reduce systematic bias and improve ranking (Vittorio et al., 2024). Prediction of sliding docking and other docking events, and docking scores, is faster and more accurate when using deep learning technologies (Sun et al., 2022). In large structure-based screens, recent AI-augmented scoring methods have improved pose accuracy and affinity prediction over traditional docking, after which MD serves as a physics gate to test pose stability, water rearrangements, and pocket binding (Salo-Ahen et al., 2020; Sun et al., 2022; Unke et al., 2021). In binding-free-energy workflows, AI-guided triage can reduce the number of expensive alchemical or QM/MM calculations while maintaining accuracy, with MD providing reference thermodynamics for calibration and correction (Clark et al., 2024; Salo-Ahen et al., 2020; Unke et al., 2021; Unke et al., 2024). However, according to Noé et al. (2020), coarse-grained molecular dynamics (MD) simulations can typically capture the thermodynamics of atomic systems well, but are

not always predictive of the correct kinetics. Baselines are generally classical docking scores, uncorrected free-energy protocols, or MD-only refinement, enabling direct comparison of AI contributions (Vittorio et al., 2024).

Theme D: Surrogate Modelling for Triage and Experiment Selection

Surrogate models approximate costly physics, such as MD-based binding free energies or quantum steps, to prioritize compounds and states under fixed compute budgets (Harren et al., 2024; Shirzadi et al., 2025). Recent active-learning frameworks combine generative design with absolute free-energy MD, using a surrogate to score candidates and update policies after each simulation round, thereby focusing high-fidelity calculations on the most informative molecules (Loeffler et al., 2024). Several deep learning models, including deep neural networks (DNNs), convolutional neural networks (CNNs), and deep confidence networks, among others, have been utilized in various domains, and in many cases, they have demonstrated a better performance than other computational models (Sun et al., 2022). Where reported, uncertainty is handled via confidence metrics or selection heuristics to reduce over-confident errors, and some studies include external or prospective checks to test generalization.

Theme E: Simulation Analysis and Feature Discovery

AI is widely applied to analyze MD trajectories, extracting low-dimensional representations, identifying kinetically meaningful states, and learning contact patterns that clarify mechanisms and guide design. Not only AI and ML technologies can increase the effectiveness of the processes, but in certain instances, they can even decrease or even eliminate the necessity of clinical trials, as they allow the use of sophisticated simulations. They also enable researchers to learn more about molecules without doing a lot of trials, hence, reducing costs and resolving ethical issues (Patel and Shah, 2022). Molecular dynamics (MD) simulation involves the calculation of the dynamics of atoms and molecules through specified force fields and initial conditions (Cui et al., 2024). Curation trajectory resources applied in GPCR studies allow the study of activation motifs and state occupancy used to design ligands (Cui et al., 2024).

Table 1: RQ1: AI methods applied to enhance MD.

Theme	Core Idea
A	AI steers MD toward rare states via learned variables/adaptive policies.
B	ML potentials replace/augment classical force fields.
C	AI rescoring/refinement reduces docking/free-energy bias.
D	Surrogates approximate costly MD/QM steps for triage.
E	AI interprets MD outputs for mechanism discovery.

RQ2 – What are the Reported Benefits and Limitations vs Classical Methods?

Theme A: Benefits – Accuracy Gains

To begin with, AI pose generators and learned scoring functions had a beneficial effect on pose selection on standard docking benchmarks, which increased the quality of structures entering short MD refinement (Corso et al., 2022; Sarkar et al., 2023; Zhou et al., 2024). The AI algorithms are important in designing new drug molecules that have better potency and selectivity. Application AI can be used to design optimized molecular structures targeting specific biological activities and also fulfilling specified pharmacological and safety criteria by deep learning models and generative adversarial networks (GANs) (Serrano et al., 2024). The benefit of this model is also that it enhances the data efficiency of the model through harnessing the alchemical information (Unke et al., 2021). Also, the ML-guided enhanced sampling was more reliable in reaching the relevant conformational states to facilitate consistent stability checks of the ligand-protein contacts before ranking (Cui et al., 2025; Qureshi et al., 2023). Across the corpus, gains were most pronounced for pose scoring and docking.

Theme B: Benefits – Efficiency and Computing Savings

Studies reported efficiency gains in three complementary ways. First, machine-learned force fields delivered accuracy at orders-of-magnitude lower cost, enabling longer or more numerous trajectories within a fixed budget (Unke et al., 2021; Unke et al., 2024). Also, AI and ML can support data cleaning and curation, identify duplicate participants, impute missing values, and standardize regulated terminology in drug development projects. They can also assist in creating metadata, masking and de-identifying personal information, and efficiently searching and retrieving stored data. These applications improve both the

accuracy of datasets and the efficiency of data processing for analysis (Niazi, 2023).

Theme C: Benefits – Decision Value and Validation

AI is a field of computer science, statistics, and engineering that uses algorithms and models to carry out tasks and demonstrate abilities such as learning, decision-making, and prediction (Niazi, 2023). Across decision points, AI can advance this trend by enhancing diagnostics, gathering personalized information, and supporting clinical decision-making (Kokudeva et al., 2024). Active-learning frameworks that integrate generative design with absolute free-energy MD demonstrated efficient selection policies and maintained accuracy while evaluating fewer compounds, supporting practical portfolio triage. Findings aligned with the pose-quality improvements reported.

Table 2: RQ2: Benefits and Limitations of AI vs Classical MD.

Theme	Core Idea
A	AI improves pose generation, scoring, and sampling.
B	ML potentials and AI preprocessing reduce cost.
C	AI supports smarter triage and portfolio choices.
D	Recurring issues across the corpus.

RQ3 – Which Therapeutic Areas Show Successful AI-Augmented MD Applications?

Theme A: Kinases

Kinase studies focus on shifts between active and inactive states, especially the DFG-in/DFG-out transition, because these motions reshape pockets and influence selectivity (Cui et al., 2025; Serrano et al., 2024; Wei and McCammon, 2024). Machine learning (ML) methods and molecular dynamics (MD) simulations are also used more frequently in de novo drug design to improve efficiency and accuracy. In addition, interpretable machine learning and deep learning methods further support this progress. By integrating AI with MD, researchers can design drugs more effectively and efficiently than before (Blanco-Gonzalez et al., 2023).

Theme B: Viral Proteins

For viral targets, workflows often combine AI-assisted docking or machine-learning triage with MD refinement to prioritize protease or polymerase inhibitors (Boniolo et al., 2021; Sun et al., 2022). Reported gains include better ranking and discrimination versus docking alone, and efficient pre-filtering of ultra-large libraries with AI before physics-based evaluation. Case studies on SARS-CoV-2 illustrate this and report stable binders after MD validation (Boniolo et al., 2021).

Theme C: GPCRs

GPCR applications rely on ensembles of receptor states in membranes; curated MD resources enable analysis of activation motifs and state occupancy relevant to design (Kaptan and Vattulainen, 2022; Wei and McCammon, 2024). Deep learning helps predict or select ligand poses and, together with MD, supports ranking at ortho-steric and allosteric sites (Sun et al., 2022). Recent work shows that studies emphasize that AI-guided ensemble docking and MD validation improve practicality when structural variability challenges single-structure screens (Serrano et al., 2024; Wei and McCammon, 2024).

RQ4 – What Gaps and Challenges Remain?

Theme A: Methodological Gaps

Conventional drug discovery relies heavily on trial-and-error testing, which is time-consuming, expensive, and often produces low accuracy. These methods are also restricted by the availability of test compounds and the difficulty of predicting their behavior in the body (Blanco-Gonzalez et al., 2023).

Theme B: Limitations of Deep Learning Models in Drug Design

Deep learning (DL) models in drug design mainly learn from observed data and often overlook the dynamic interactions between proteins and ligands. Molecular dynamics (MD) simulations address this gap by capturing protein conformations, interaction evolutions, and complex processes such as protein folding. Unlike standard docking approaches, MD can account for conformational changes during ligand binding, helping to overcome key limitations of structure-based drug design (SBDD) (Sun et al., 2022).

DISCUSSION

This study aimed to systematically assess how AI methods have been integrated with molecular dynamics simulations for fostering inhibitor discovery and therapeutic development. The researcher has also focused on identifying methodological innovations, benefits compared with classical approaches, therapeutic applications, and remaining gaps. In relation to RQ1, there are various distinct

AI strategies which have emerged in the prior literature. Past studies have demonstrated that machine learning can direct MD trajectories toward functionally relevant conformations. However, studies show that reinforcement learning frameworks and adaptive neural networks significantly reduced the timescales which is required for observing the rare transitions (Kleiman and Shukla, 2022; Shin et al., 2019). These findings are consistent with the prior research, which noted that enhanced sampling using AI captures metastable states with greater efficiency as compared to the unbiased long-timescale MD (Mehdi et al., 2022; Tian et al., 2022). Similarly, results also revealed that machine-learned force fields and neural network potentials provide near ab initio accuracy at reduced computational cost (Unke et al., 2021). Researchers demonstrated the reinforcement learning frameworks in combination with MD for de novo molecule design and drug response prediction (Atance et al., 2022). Researchers also agree that ML is capable of generalizing across chemical space while maintaining quantum-level precision. These findings also resonate with the performance of ANI models, which have been shown to extend to drug-like molecules (Lahey et al., 2020; Yang et al., 2024). Graph neural networks and hybrid ML-physics approaches have been shown to improve docking and free-energy predictions, as they can reduce the false positives (Cain et al., 2022).

Regarding RQ2, there are main categories of benefits and limitations that were evident in the results. Accuracy gains were frequently reported. In this regard, ML force fields reduce systematic errors, and AI-assisted sampling uncovers biologically relevant conformers overlooked by conventional MD (Boniolo et al., 2021). Such improvements also align with the findings of prior researchers who showed that ML-based enhancements are important in improving the structural accuracy and binding predictions (Min et al., 2024). Efficiency and computing savings are also equally significant, as studies demonstrated that AI approaches achieved quantum-level accuracy with orders of magnitude lower computational resources (Unke et al., 2022). These benefits also align with wider claims that AI provides predictive accuracy and actionable insights for drug design (Moingeon et al., 2022). However, notable limitations temper these advances. However, there are various challenges which are evident in the past literature. Researchers underscored that AI in drug discovery often suffers from poor reproducibility and inadequate reporting of uncertainty. Thus, AI-augmented MD offers clear improvements in accuracy, efficiency, and decision support, but its credibility and translational potential are constrained by methodological limitations and data biases.

With respect to RQ3, therapeutic applications clustered around kinases, viral proteins, and GPCRs. For kinases, results also depicted that AI classifiers combined with MD captured conformational transitions. Researchers argue that dynamic solvent networks lead to differential kinase inhibition and cannot be captured by static docking alone (Lee et al., 2018). Viral protein studies also consider AI docking integrated with MD so that the inhibitors can be optimized for viral proteases and polymerases (Varghese et al., 2025). It shows broader evidence that AI-assisted docking accelerated antiviral discovery during COVID-19. GPCR plasticity poses major challenges for conventional docking and can be addressed through dynamic ensemble methods. However, these applications suggest that AI-MD integration adapts successfully across therapeutic classes.

RQ4 also showed key gaps and challenges that must be addressed for broader adoption. Methodological gaps involved the lack of consensus protocols for benchmarking AI-MD methods and insufficient external validation across diverse protein classes. Data and benchmarking gaps are also evident, as researchers focused on the scarcity of standardized, target-stratified datasets that integrate MD trajectories with experimentally validated binding data. This aligns with FAIR-data advocacy (Korlepara et al., 2024; Liu et al., 2025) It stresses that interoperable datasets are critical for reproducibility and cross-study comparability. Validation and translation gaps were perhaps the most prominent, as few studies extended computational results to experimental pipelines or clinical evaluation. It also raises important concerns regarding the real-world impact of current methods (Li et al., 2024; Wang et al., 2022). Thus, it is important to address these challenges that will require community-wide efforts in benchmark development, data sharing, and reproducibility standards.

RESEARCH IMPLICATIONS

Theoretical implications

The results of this review were important in providing several theoretical contributions to the growing body of literature regarding AI integration with molecular dynamics (MD). The findings extend computational drug discovery theories as they show that AI does not replace physics-based models but enhances them. It is evident through guided sampling, machine-learned force fields, and surrogate modeling. This suggests a hybrid paradigm where predictive accuracy originates from both physics-grounded and data-driven approaches. As a result, existing theoretical models of molecular recognition and binding can be enhanced.

From a theoretical viewpoint, this also contributes to a broader understanding regarding protein–ligand dynamics, as AI-enhanced MD provides evidence that solvent effects, conformational flexibility, and hidden states can be systematically incorporated into mechanistic explanations of inhibition (Gupta et al., 2022). Thus, the findings also call for refining theoretical frameworks to integrate principles of transparency, interpretability, and generalizability. Thus, the review expands conceptual boundaries as it positions AI-MD as a methodological tool and as a new theoretical lens for understanding the dynamics of molecular interactions in drug discovery.

Practical Implications

From a practical perspective, the review underscores that there are important implications for researchers, industry practitioners, and policymakers. The benefits of AI-MD integration play an important role in improving accuracy, efficiency, and decision-making value (Prašnikar et al., 2024). It suggests that pharmaceutical pipelines can be optimized through the integration of hybrid models for lead identification and prioritization. For therapeutic applications, particularly in viral proteins and GPCRs, AI-MD are important in providing tools which can explore the conformational changes that are inaccessible to static docking. As a result, inhibitor selectivity and effectiveness can be improved. At the same time, the reported challenges also highlight the need for industry-wide practices that emphasize reproducibility, standardized benchmarks, and open data sharing. It implies that investments in AI should be paired with transparent protocols and cross-validation against experimental assays so that the reliability can be ensured. Policymakers and funding agencies can also use these insights to support their initiatives around FAIR data and reproducibility standards. It enables broader access and comparability across studies. Practically, the review underscores that AI-MD has transformative potential for drug discovery. However, its impact will depend on community-wide collaboration, open resources, and rigorous translation into experimental and clinical contexts.

LIMITATIONS AND FUTURE RESEARCH INDICATIONS

This review is limited by the scope of included studies. The review was restricted to peer-reviewed articles and may not fully capture unpublished or proprietary AI-MD applications currently under development in the pharmaceutical industry. Another limitation is the variability in methodological detail and benchmarking across the reviewed studies. It constrained the direct comparisons and can also introduce bias in interpreting the reported benefits. Future research can focus on prioritizing the development of standardized benchmarks, interoperable datasets, and reproducible workflows so that comparability can be improved. Moreover, greater integration of experimental validation and clinical translation is required to bridge computational predictions with therapeutic outcomes. Expanding applications beyond the studied targets and investigating explainable AI models will also be critical for advancing both scientific credibility and real-world adoption.

CONCLUSION

This study aimed to systematically review how AI methods have been integrated with molecular dynamics simulations to foster inhibitor discovery and therapeutic development. The findings showed that AI enhances MD through guided sampling, machine-learned force fields, refined scoring, and surrogate modelling. It offers improvements in accuracy, efficiency, and decision value as compared with classical approaches. In this context, AI-MD integration provided insights regarding the conformational dynamics and improved prioritization of drug candidates. However, significant challenges remain evident, which include methodological gaps, limited benchmarking resources, and insufficient experimental validation. It also constrains broader adoption. Overall, this review highlights that AI augments rather than replaces MD. It positions hybrid approaches as powerful tools for drug discovery. Future progress can be focused on addressing reproducibility and data-sharing challenges so that computational advances translate effectively into clinical and therapeutic contexts.

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CONFLICT OF INTEREST STATEMENT

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

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception, design, and development of this manuscript. [Author 1] was

primarily responsible for literature collection and data organization. [Author 2] contributed to data analysis and thematic synthesis. [Author 3] worked on drafting the manuscript and integrating revisions. [Author 4] supervised the project, provided critical feedback, and finalized the manuscript. All authors reviewed and approved the final version of the manuscript.

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