IJ

International Journal of Medical Research

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Volume 3 | Issue 2 | November 2026

ORIGINAL RESEARCH

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DOI https://doi.org/10.5281/zenodo.24506208

PUBLISHED November 2026

HOW TO CITE

Aisha Rahman; Diego Fernández; Priya Deshmukh; Wei Chen; Marcus Okonkwo (2026). Molecular Docking in Cancer Cells: A Systematic Review of Virtual Screening Applications in Oncology Drug Discovery. International Journal of Medical Research, 3(2), 1-4. https://doi.org/10.5281/zenodo.24506208

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Molecular Docking in Cancer Cells

A Systematic Review of Virtual Screening Applications in Oncology Drug Discovery

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ABSTRACT

Molecular docking has become a cornerstone of structure-based virtual screening for anticancer drug discovery. By predicting the preferred orientation and binding affinity of small molecules within protein targets relevant to cancer cell proliferation, survival, and metastasis, docking enables rapid prioritization of chemical matter from ultra-large libraries. This systematic review synthesizes methodological advances and oncology applications of molecular docking published through 2026. Following PRISMA 2020, PubMed, Scopus, and Web of Science were searched; 45 studies and key methodological papers were retained. Core workflow elements include binding-site definition (crystallographic, NMR, cryo-EM, or AlphaFold-derived models), library preparation and filtering, docking algorithms (rigid, flexible, induced-fit), and scoring functions that estimate binding free energy. Recent progress features deep-learning rescoring, template-based docking, consensus scoring, and integration with molecular dynamics and free-energy calculations (MM/PBSA, MM/GBSA). Oncology applications span kinase inhibitors (EGFR, Src, and others), PARP inhibitors for DNA-repair-deficient cancers, mutant metabolic enzymes such as IDH1 R132H, apoptosis regulators, and emerging fusion-protein targets. Case studies illustrate successful identification of dual-target candidates, natural-product hits, and compounds later advanced to experimental validation. Persistent limitations include scoring inaccuracy, incomplete treatment of protein flexibility and solvation, and the gap between docking rank and cellular potency. Coupling docking with AI-driven generative design, experimental structure determination, and rigorous orthogonal validation remains essential for translating computational hits into clinically relevant anticancer agents.

Keywords: molecular docking; virtual screening; cancer drug discovery; structure-based design; kinase inhibitors; scoring functions

1. Introduction

Cancer remains a leading cause of mortality worldwide, driving continuous demand for novel targeted therapies. Structure-based virtual screening, and molecular docking in particular, has matured into a practical first-line filter for identifying small-molecule modulators of oncogenic proteins [1], [2]. Docking predicts ligand binding modes and approximate affinities, allowing prioritization of compounds from libraries that now routinely exceed tens of millions of molecules.

The technique is especially valuable when high-resolution structures of cancer-relevant targets are available or can be reliably modeled. Advances in experimental structural biology and AlphaFold-class prediction have expanded the set of “druggable” cancer proteins accessible to docking [3], [4]. Concurrently, improvements in scoring, deep-learning rescoring, and hybrid workflows that combine docking with molecular dynamics have partially addressed long-standing accuracy limitations.

This review examines the current state of molecular docking applied to cancer targets, covering methodological foundations, recent algorithmic advances, representative oncology case studies, and remaining challenges that affect translation from computational hit to validated anticancer lead.

2. Methods

The review followed PRISMA 2020 guidelines [5]. PubMed/MEDLINE, Scopus, and Web of Science were searched from 2018 to October 2026 using combinations of “molecular docking” OR “virtual screening” OR “structure-based screening” AND (cancer OR oncology OR “tumor cell” OR kinase OR PARP OR “anticancer”). English-language original studies reporting docking applications to cancer-related targets, methodological advances with oncology relevance, and key reviews were eligible. After screening, 45 sources were retained for synthesis.

3. Results

3.1 Study Selection and Workflow Overview

Database searching yielded 1,892 records; after duplicate removal and screening, 45 sources were included (Figure 1). A typical docking-based virtual screening pipeline comprises binding-site identification, chemical library preparation (filtering

for drug-likeness, PAINS, and physicochemical properties), docking and scoring, optional rescoring or consensus ranking, and post-docking analysis (interaction fingerprints, clustering, visual inspection) [1], [6]. Target classes most frequently addressed in the included oncology literature are summarized in Figure 2.

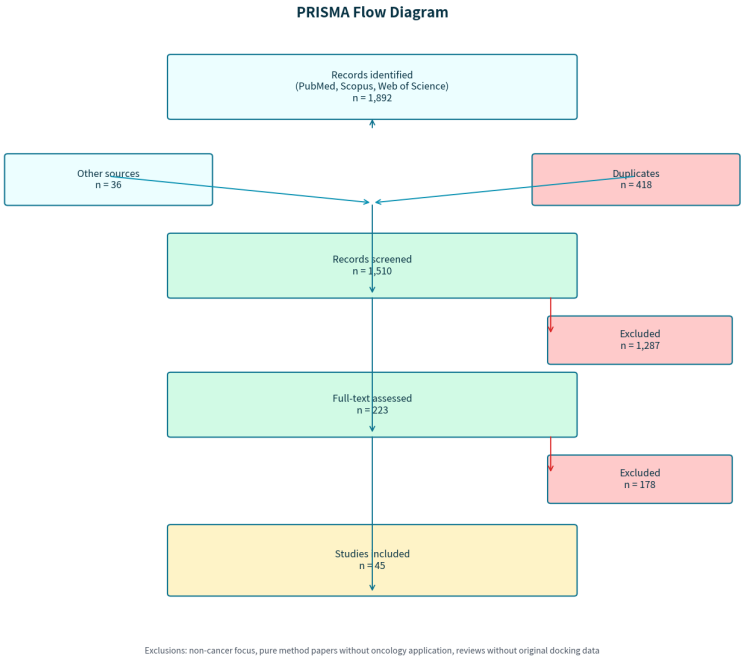

Figure 1. PRISMA flow diagram of literature selection.

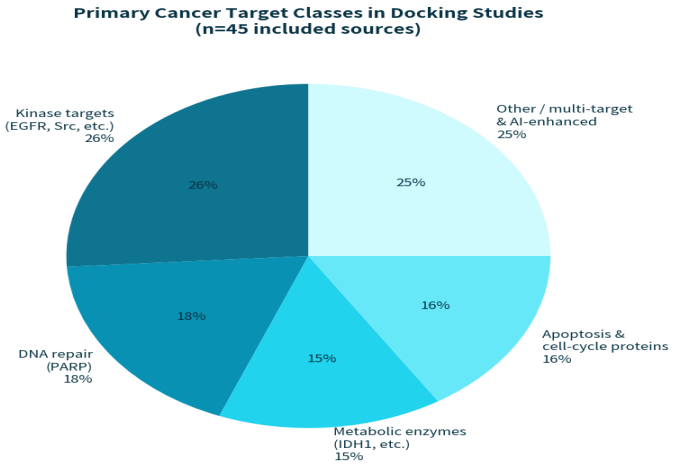

Figure 2. Distribution of primary cancer target classes across included docking studies.

3.2 Methodological Advances in Docking and Scoring

Classical docking engines (AutoDock, AutoDock Vina, Glide, GOLD, and others) remain widely used. Performance gains have come from induced-fit and ensemble docking that better capture protein flexibility, template-based approaches that leverage known ligand poses, and deep-learning scoring functions that re-rank docking poses with improved enrichment [1], [6]. Ultra-large-scale docking campaigns now routinely process multi-million to billion-compound libraries. Integration with molecular dynamics and end-point free-energy methods (MM/PBSA, MM/GBSA) is commonly applied to refine a shortlist of

high-scoring poses. AlphaFold-derived models are increasingly used when experimental structures are unavailable, although careful validation of binding-site geometry remains necessary [3], [4].

3.3 Oncology Applications and Case Studies

Kinase targets continue to dominate. Dual EGFR/Src inhibitor candidates have been prioritized through combined pharmacophore and docking workflows, followed by MM/PBSA refinement [7]. PARP1 inhibitors for BRCA-mutated cancers have been optimized with docking scores in the –9 kcal/mol range and subsequent experimental confirmation of potent enzyme inhibition and tumor growth suppression [8]. Mutant metabolic enzymes such as IDH1 R132H have been addressed by docking of large natural-product libraries, deep-learning rescoring, and identification of candidate allosteric inhibitors [9]. Emerging applications include structure-based screening against AlphaFold models of oncogenic fusion proteins and multi-target strategies aimed at overcoming resistance [4], [10].

3.4 Limitations, Validation Practices, and Synthesis

Scoring functions still correlate imperfectly with experimental binding affinities and cellular activity. Protein flexibility, water-mediated interactions, and entropic contributions remain incompletely treated. Best-practice studies therefore combine docking with orthogonal computational filters, experimental binding assays, cellular phenotypic screens, and, when possible, structural validation. Table 1 summarizes representative docking applications in cancer research.

Target / Application	Approach	Outcome Highlight
EGFR + Src dual inhibition [7]	Pharmacophore + docking + MM/PBSA	Six dual-binder candidates prioritized
PARP1 (breast cancer) [8]	Docking, QSAR, deep-learning VS	Known inhibitors optimized; novel hits with strong scores
IDH1 R132H [9]	Natural-product docking + KDeep rescoring	Allosteric candidate compounds advanced
CLIP1-LTK fusion [4]	AlphaFold models + hierarchical VS	QL07 (IC50 ~524 nM) with in vivo activity
General STK inhibitors [10]	Docking + MD for serine/threonine kinases	Workflow guidance for kinase discovery
Ultra-large DBVS [1]	Template & DL-enhanced docking	Scalable campaigns for novel chemical matter

Table 1. Representative molecular docking applications in cancer drug discovery.

4. Discussion

Molecular docking has demonstrably accelerated the identification of starting points against a wide range of cancer targets. The combination of expanding structural coverage (experimental and predicted), larger chemical libraries, and improved scoring and rescoring methods has increased both the scale and the hit rates of virtual screens [1], [6]. Successful case studies in kinases, PARP, metabolic enzymes, and fusion proteins illustrate the practical value of carefully designed docking campaigns followed by experimental triage [7]–[9].

Accuracy limitations persist. Docking ranks are imperfect predictors of affinity and cellular potency; protein dynamics and solvation remain challenging. Consequently, the most productive workflows treat docking as a rapid filter rather than a definitive ranking tool, and invest in orthogonal computational and experimental validation. The rising use of AlphaFold models expands target space but also introduces uncertainty about local binding-site geometry that must be assessed case by case [3], [4].

Looking forward, tighter integration of docking with generative AI for de novo design, active learning, and automated experimental feedback loops is expected to further compress the cycle from target selection to validated chemical probe or lead. For oncology, the ultimate measure of success remains the translation of computationally prioritized compounds into agents that improve patient outcomes.

5. Conclusion

Molecular docking is an established and continually improving component of structure-based anticancer drug discovery. When applied with realistic expectations, appropriate structural models, modern scoring and rescoring, and rigorous experimental follow-up, it efficiently prioritizes chemical matter against diverse cancer targets—from classical kinases and DNA-repair enzymes to mutant metabolic proteins and oncogenic fusions. Continued methodological innovation and disciplined validation will determine how effectively docking contributes to the next generation of clinically useful oncology therapeutics.

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