Archives of Pharmaceutical Sciences and Research E-ISSN 0975-2633 | PRINT ISSN 0975-5284
Vol 16 Issue 2 14-21 June 2026 Review Article

MOLECULAR DOCKING APPROACHES FOR DRUG REPURPOSING AGAINST NDM-1 (NEW DELHI METALLO -B-LACTAMASE-1) IN *ESCHERICHIA COLI*

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ABSTRACT

Increasing levels of antibiotic resistance worldwide, with NDM-1 producing *E. coli* strains being one of the most challenging pathogens to treat.NDM-1 enzyme is a zinc-dependent metallo-β-lactamase that hydrolyzes all classes of β-lactam antibiotic, even carbapenems, which are the reserved drugs to combat antibiotics. Therefore, drug repurposing approaches have proven extremely effective for detecting potential inhibitors from pharmacologically validated drugs. This article reviews the importance of molecular docking as a fundamental tool in drug repurposing approaches for NDM-1 inhibition. In particular, high-throughput screening is gaining greater recognition in the field virtual screening of FDA-approved drug libraries, allowing for immediate evaluation of key initiatives with candidate molecules with favorable pharmacokinetic and safety profiles. Docking approaches, scoring function theories, and virtual screening techniques are reviewed in detail for their capability in predicting drug-enzyme binding interactions. Further, the connection of docking with other computational methods like molecular dynamics simulation, pharmacophore generation, and artificial intelligence-based approaches has led to improve the ability to locate. Particularly there are several of repurposing agents that show promising binding affinity to the NDM-1 activity site via binding to catalytic zinc ions. In spite of that, issues related to scoring functions, lack of protein flexibility, and experimental validation persist as barriers to translation. In the review, an extensive and critical overview of advances, limitations, and prospects in the field is provided, emphasizing the need for integrated computational-experimental approaches in drug development.

KEYWORDS: Molecular Docking, *Escherichia coli,* Drug Repurposing, New Delhi metallo-β-lactamase-1, Antibiotic Resistance.

INTRODUCTION

Among reasons behind rising global health concerns stands reduced effectiveness of antibiotics. When multidrug-resistant microbes advance and treatment options shrink, healthcare facilities face mounting adjustments. Known widely for triggering illness across diverse groups, *Escherichia coli* appears often in clinical settings. Effective management has become increasingly challenging due to the difficulty of dealing with its resistant strains. (Dolui et al., 2021; Shailaja et al., 2021).

E. coli contains New Delhi metallo-β-lactamase-1 (NDM-1), which lowers the efficacy of many β-lactam medicines, including carbapenems. Diminished effectiveness results in more difficult clinical judgments because these medications are frequently the last resort. Genetic components that can travel between microorganisms permit the appearance of NDM-1 in a variety of microorganisms. Spread persists through common DNA regions even as therapy becomes more challenging. (Li et al., 2020; Shailaja et al., 2021; Dolui et al., 2021).

NDM-1 uses a metal-dependent catalytic mechanism to operate at the molecular level. Zinc ions in the antibiotic's active site activate water molecules that cleave the β-lactam ring, considerably facilitating antibiotic degradation. This metal ion dependence makes NDM-1 a challenging but important target for inhibitor development. (Tolbatov and Marrone, 2020).

Drug repurposing has become a popular method in recent years for finding new therapeutic applications for already-approved medications. This method increases the likelihood of clinical success while saving time and money when compared to traditional drug discovery. In this approach, molecular docking has emerged as a crucial method that enables the identification of molecules with great binding affinity toward NDM-1 and the prediction of ligand–protein interactions. (Bhagat et al.,2020; Huang et al.,2020).

Additionally, advanced computational methods like molecular dynamics simulations, pharmacophore modeling, and virtual screening have improved the effectiveness of finding possible inhibitors. In order to find potential candidates against NDM-1, these combined techniques have been widely used in recent

studies. (Alkhatabi and Alatyb, 2021; Valencia et al., 2021).

Furthermore, the precision of scoring algorithms and the appropriate choice of computational tools are critical to the efficacy of molecular docking in medication repurposing. It is crucial to carefully interpret data because studies have demonstrated that differences in docking software and protein targets can greatly affect binding predictions. (Ivanova and Karelson, 2021). Furthermore, it has been demonstrated that integrating docking with complementary methods like binding energy calculations and molecular dynamics simulations increases the accuracy of projected interactions. These combined methods aid in the prioritization of possible inhibitors for experimental validation in addition to offering improved insights into ligand stability. (Rehman et al., 2021; Valencia et al., 2021).

The objective of this review is to critically examine molecular docking techniques employed in drug repurposing against NDM-1 in *Escherichia coli*, with an emphasis on current issues, important discoveries, and recent developments.

Biology of NDM1

The metallo-β-lactamase enzyme NDM-1 can interact with a wide range of β-lactam antibiotics due to its very flexible and adaptable active site. Its broad-spectrum resistance capabilities is a result of its structural flexibility, which also makes inhibitor creation extremely difficult. Both the structural stability and catalytic activity of the enzyme depend on its binuclear zinc core. (Li et al.,2020)

The drug's β-lactam ring is then attacked by this activated water molecule, causing hydrolysis and decreasing the antibacterial efficacy of the medication. Inhibitors that can disrupt zinc coordination have demonstrated encouraging outcomes in lowering enzyme activity due to this metal-dependent mechanism. (Tolbatov and Marrone,2020).

Additional variants with improved stability and resistance have also emerged as a result of mutations and structural changes in NDM-1. These variations emphasize the necessity for flexible and adaptive inhibitor design approaches and further complicate treatment strategies. (Farhat and Khan,2024)

Drug Repurposing in NDM1

Since there are currently no clinically approved inhibitors for NDM-1, drug repurposing has drawn a lot of attention as a tactic to fight antimicrobial resistance. This strategy reduces the time and expense involved in drug development by utilizing current medications with established pharmacokinetic and safety profiles. (Shailaja et al., 2021).

Drug repurposing and molecular docking have been effectively used in a number of studies to find possible NDM-1 inhibitors. Compounds that can successfully bind to the active site of an enzyme and interfere with its function have been found using virtual screening of FDA-approved drug libraries. These substances frequently interact with metal ions and important residues that are essential for enzymatic function (Dolui et al., 2021). Additionally, natural substances and bacterial metabolites have been investigated as possible inhibitors. These compounds offer a wide range of chemical space and have demonstrated stability and good binding affinity in computational experiments, making them attractive options for future research. (Alotaibi et al., 2025).

Molecular Docking Approaches

A computational technique called molecular docking is used to anticipate a ligand's preferred orientation when it binds to a target protein. By determining important chemical interactions and predicting binding affinity, it is essential to structure-based medication design. A search algorithm to investigate potential conformations and a scoring system to rank binding poses are the two primary components of docking approaches. (Bhagat et al., 2020; Ahmad et al., 2020).

Rigid docking and flexible docking are the two main categories of docking techniques. While rigid docking assumes a steady structure, flexible docking permits conformational fluctuations, improving prediction accuracy of protein structure. However, more flexibility also drives up computation costs. (Bhagat et al., 2020).

Although scoring functions are an essential part of docking, their accuracy is still a significant problem. To assess binding affinity, a variety of scoring functions have been developed, including force-field-based, empirical, and knowledge-based approaches. Despite these developments, consensus scoring techniques are frequently employed to increase prediction accuracy because no single scoring function yields consistently accurate results. (Huang et al., 2020).

The selection of software and the properties of the target protein have a significant impact on docking performance. Due to variations in search methods and scoring processes, several docking technologies, including Auto Dock, Auto Dock Vina, and Glide, frequently yield different results. Research has demonstrated that widely used metrics, such as ligand efficiency and binding energy, are not always accurate and can change based on the computational settings and protein structure. Furthermore, docking accuracy is greatly impacted by elements such appropriate ligand preparation, protonation state, and hydrogen addition, underscoring the necessity of meticulous protocol development and validation (Ivanova and Karelson, 2022; Singh et al., 2021)

Integrated Modeling Approaches for Protein-Ligand Analysis

In order to increase prediction reliability, recent research highlights the need of integrating molecular docking with other computational methods. Virtual screening enables the quick review of huge compound libraries, while pharmacophore modeling helps in identifying crucial characteristics needed for ligand binding. (Alkhatabi and Alatyb, 2021).

By evaluating the stability of ligand–protein complexes over time, molecular dynamics simulations improve docking studies even further. This method helps validate docking data and offers insights into dynamic interactions. According to a number of studies, chemicals found by combining docking and MD simulations show significant inhibitory capability against NDM-1 and stable binding. (Valencia et al., 2021; Rehman et al., 2021).

Finding new inhibitors from big chemical databases has also been accomplished with high-throughput virtual screening. For example, compounds with high binding affinities and positive interactions with important active site residues have been found through screening of ZINC database chemicals. (Rehman et al., 2021).

In addition to these approaches, recent advancements demonstrate the growing significance of artificial intelligence and improved scoring methodologies in enhancing docking accuracy. The inability of traditional scoring methods to consistently rank ligand binding affinities can result in inconsistent predictions of effective inhibitors. In order to improve prediction reliability by incorporating several evaluation factors, consensus scoring and machine learning-based models have been created. (Huang et al., 2021; Ivanova and Karelson, 2022).

Also, recently developed deep learning frameworks such as diffusion-based docking models demonstrate improved accuracy and efficiency by treating ligand binding as a generative process instead of a fixed prediction problem.

Also, recently developed deep learning frameworks such as diffusion-based docking models demonstrate improved accuracy and efficiency by treating ligand binding as a generative process instead of a fixed prediction problem. These findings suggest that the identification of potential NDM-1 inhibitors can be greatly improved by combining advanced computational methods with traditional docking approaches. (Corso et al., 2022).

Comparative Evaluation of Docking and Repurposing Strategies

Several computational techniques have been used in various investigations to find possible NDM-1 inhibitors. Because drug repurposing techniques rely on molecules with established safety profiles, they are especially beneficial because they can speed up clinical translation. Novel compound screening, on the other hand, provides greater chemical variety and the potential to find whole new inhibitor scaffolds. Interestingly, integrated techniques that include molecular docking, molecular dynamics simulations, and experimental validation have found viable candidates more frequently. (Dolui

et al., 2021; Rehman et al., 2021).

However, a number of variables, such as software selection, scoring methods, and the target protein's structural features, affect how accurate docking-based predictions are. Research demonstrates that binding energy values by themselves are insufficient for accurate candidate selection, highlighting the importance of additional validation techniques and careful result interpretation.(Ivanova and Karelson, 2022).

Benchmarking evaluations further show that while docking techniques can produce feasible binding conformations, they frequently have difficulty accurately ranking these poses. This drawback highlights the necessity of better scoring methods and the incorporation of various computational approaches to increase forecast performance (Singh et al., 2021).

Molecular docking is a useful initial technique for finding possible NDM-1 inhibitors, according to the reviewed literature. Strategies for repurposing drugs, in particular, have great potential because they are less expensive and need shorter development times. Favourable binding interactions with important active site residues, such as coordination with zinc ions essential for enzyme activity, are displayed by a number of discovered compounds.

Challenges and Limitations of Molecular Docking Approaches

Molecular docking techniques have several inherent limitations that reduce prediction accuracy despite significant progress. The inability of scoring functions to accurately rank ligand poses and estimate binding affinity is one of the main problems. It is also challenging to develop broad selection criteria for possible inhibitors because different target protein structures and docking methods produce varied results**.** (Huang et al., 2020; Ivanova and Karelson, 2022).

Another major disadvantage of docking is its static portrayal of protein–ligand interactions and its inability to correctly capture the dynamic dynamics of biological systems. As a result, anticipated binding conformations may not accurately reflect real-time stability inside the active site. Integrated methods that combine molecular docking with molecular dynamics simulations and experimental validation have been widely used to address these problems, offering increased dependability and a more thorough understanding of contact stability. (Valencia et al., 2021; Rehman et al., 2021).

Molecular docking techniques are used extensively in computational drug discovery for predicting the interaction between ligands and proteins as targets; there are, however, several drawbacks of these techniques that impact their accuracy. The main disadvantage in most molecular docking methods is the assumption that the protein is rigid. Proteins, as we know, are flexible macromolecules, and their conformational change is essential during the process of ligand binding. This limitation affects the accuracy of binding mode prediction, especially for those proteins that have flexible active sites. Moreover, the scoring techniques employed in these methods are simplistic and may cause errors in the ranking of the prospective drugs. (Meng et al., 2011).

Another critical drawback of molecular docking techniques is their incapacity to incorporate solvent effects and metal ions' contributions. Water molecules play a crucial role in regulating how proteins and ligands interact, yet most docking methods ignore or undervalue their contributions. In situations like NDM-1, where zinc (Zn^{2+}) is essential to its operation, such deficiency is particularly critical. Additionally, even while docking software makes an effort to account for ligand flexibility, it is unable to identify the most advantageous binding orientation since it does not explore all possibility inside the conformational space. (Morris et al., 2009).

In addition to the mentioned above, the use of molecular docking methods only allows one to obtain a static image of protein-ligand interaction, not showing the dynamics of these processes inherent to all biological systems. This makes molecular docking methods incapable of providing information on complex stability during physiological processes. The problem of lack of dynamic information can be solved by using molecular dynamics methods. The second problem with the use of molecular docking is that the reliability of results depends on the quality of initial data used for

calculations. (Mazumder et al., 2025).

Lastly, there is an absence of any biological evidence with regard to molecular docking methodologies, which need to be taken into account while interpreting their results. Binding affinity is often a good predictor of biological activity, but in the case of docking methodologies, it is worth keeping in mind that pharmacological, toxicological, and bioavailability aspects are ignored. In addition, many research papers focus only on the scores of docking approaches and use them for compound ranking; however, this approach might result in false prioritization of molecules. (Tarín-Pelló et al., 2022; Shi et al., 2021).

Gaps in Current Research

Finding strong NDM-1 inhibitors is still difficult, despite improvements in virtual screening and repurposing older drugs. Although computational research has produced encouraging results, no NDM-1 medication has received formal approval. (Li et al., 2022; Farhat and Khan, 2024).

It is challenging to trust scoring functions' binding affinity predictions because they frequently misrank ligand poses. This defect makes docking difficult to use on its own for virtual screening. Current techniques frequently overlook protein mobility, which affects our understanding of molecular interactions. Predicted bound ligand shapes become less reliable if such action is not taken into consideration. (Huang et al., 2020; Singh et al., 2021; Ahmad et al., 2020).

Also, while a number of possible inhibitors have been found using computational techniques like docking and virtual screening, only a small number of studies have included experimental validation, limiting their translational usefulness. (Rehman et al., 2021; Dolui et al., 2021).

In order to overcome these drawbacks, computational methods must be improved. More precise scoring models that take into consideration the movement of proteins must be used, and lab-based testing must be tightly linked to the development of NDM-1 inhibitors that function in actual clinical settings. Even if development is still unequal, it depends on combining empirical checks with dynamic simulations to make sure designs go beyond theory and become workable solutions where they are most required.

Artificial intelligence has the potential to improve ligand selection using machine learning techniques. These methods could improve molecule binding prediction accuracy. These techniques also make it possible to speed up the search for potent NDM-1 blockers. (Huang et al., 2020; Corso et al., 2022).

RESULTS AND DISCUSSION

Together, all the studies mentioned above clearly show that computational analysis has an important role in finding the possible inhibitors of NDM-1 in E. coli. All the researches conducted in this direction utilize molecular docking and virtual screening to investigate the interaction between the protein and ligand in terms of binding energy and the strength of interaction. Some of the articles have mentioned compounds that can bind effectively to the protein with binding energy from -7 to -11 kcal/mol (Rehman et al., 2021; Valencia et al., 2021). However, the mere binding energy cannot be considered as the sole indicator of inhibition capability of ligands due to their interaction pattern with the protein.

In-depth examination of protein-ligand binding reveals the significance of certain residues at the active site, namely, His120, His122, Asp124, and His189, which are commonly engaged in ligand binding processes in various research works (Valencia et al., 2021; Rehman et al., 2021).

Apart from these residues, binuclear Zn^{2+} metal ions play an essential role in the catalysis process of NDM-1. Research has demonstrated that ligands that coordinate to these zinc metal ions possess stronger inhibitory capacity since they inhibit enzyme catalysis rather than forming tight binding sites (Tolbatov and Marrone, 2020).

Repurposing techniques for drugs have been researched thoroughly and exhibited promising results towards the identification of NDM-1 inhibitors. Virtual screenings discovered several candidates with favorable interaction and binding profile through large databases of

chemicals like ZINC (Rehman et al., 2021; Doluia et al., 2021).

Repurposed drugs possess many advantages owing to their well-defined pharmacodynamics and safety, thereby speeding up the clinical process. Simultaneously, research on natural drugs and flavonoids like morin have displayed potent inhibition activities along with existing antibiotic drugs such as meropenem against the NDM-1 producing bacteria of E. coli (Ren et al., 2023).

Even though the docking study yielded positive results, the ADMET analysis provided evidence that not all the compounds can be used as drugs. Computer-aided simulations of cyclic borate derivatives and chromones confirmed that even though certain molecules had high affinity for binding to receptors, they differed widely regarding their pharmacokinetics (Cristancho et al., 2022).

Some molecules did not satisfy one criterion or another concerning absorption, availability, or toxicity, which meant that the docking results should be considered together with ADMET analysis.

In order to make docking prediction more reliable, a number of works included molecular dynamics (MD) simulation to analyze the stability of ligand-protein interactions over time. MD simulations helped determine the flexibility and stability of interactions not accounted for by static docking methods (Valencia et al., 2021; Rehman et al., 2021).

Structures showing stable RMSD and stable interactions during MD simulation appeared to be more perspective inhibitors. Pharmacophore-based approach to molecular docking also allowed identifying structural characteristics necessary for efficient binding (Alkhatabi and Alatyb, 2021).

With respect to computational methods such as docking, virtual screening, and machine learning, developments have made the drug discovery process even more efficient. Virtual screening of large databases of chemicals can help identify candidate drugs quickly, while advances in computational algorithms ensure that predictions are more accurate due to the consideration of many other factors apart from the scoring function (Doluia et al., 2021).

Nevertheless, several disadvantages of molecular docking have been noticed. The first important one is that there is an assumption that proteins are rigid molecules however, this is wrong because proteins do not behave in this way. It means that it will be impossible to predict the right binding modes and interaction. Besides, there may be differences between various software, which makes it hard to compare results. stability (Valencia et al., 2021).

However, one more thing worth considering is that binding energies do not necessarily correlate with inhibitions in experiments. Among other things, metabolism, toxicity, and permeability may affect the efficiency of the drug. Therefore, the prediction model remains just an initial attempt that needs to be verified experimentally (Cristancho et al., 2022).

In general, the literature review presented above shows that molecular docking is an essential first step towards the identification of novel NDM-1 inhibitors. The drug repositioning technique and natural products prove to be efficient, particularly when combined with computational approaches. ADME/Tox analysis, molecular dynamics simulation, and pharmacophore modeling enhance the reliability of prediction. Nevertheless, the drawbacks associated with docking make it imperative to adopt a dual approach in identifying effective NDM-1 inhibitors.

CONCLUSION

Molecular docking has proven to be a fundamental stage in identifying inhibitors of NDM-1 in *Escherichia coli* through a highly effective approach in terms of both time and money. Through the use of medicines that have already been confirmed safe, one can considerably reduce the time spent on bringing them to practical application. Currently, the most promising medicines inhibit NDM-1 by forming complexes with zinc or affecting the active site of the enzyme. Yet the major disadvantage is inherent in the fact that the technique docking is rather rigid and does not take into consideration such factors as the contribution of metals or solvent. (pushpakom et al., 2019; Kitchen et al., 2004).

Moving forward, research efforts for designing NDM-1 inhibitors will increasingly rely on the utilization of advanced computational algorithms, including deep learning approaches and diffusion models, where binding of the ligands is viewed as generative task. Moving forward, it is important that future studies overcome the drawbacks of traditional scoring through the use of machine learning methods and consensus scoring. In addition, it will be highly beneficial to search the chemical space of natural products and bacterial metabolites in addition to FDA approved compound libraries. Finally, the most critical aspects will involve closing the computational-experimental gap through focusing on a drug candidate's profile that includes factors such as toxicity and bioavailability (Daina et al., 2017; Wan et al., 2015).

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