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REVIEW ON MOLECULAR DOCKING IN DRUG DESIGN AND DISCOVERY

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ABSTRACT

The field of computer aided drug design and discovery (CADDD) is a rapidly growing area that has seen many successes in the last few years. Many giant pharmaceutical companies, in addition to academia, adopt CADDD for drug lead discovery. The explosion of structural informatics, genomics and proteomic plays a major role in leading the efforts towards modern era drug discovery and development. Enormous research from the last two decades has been pursued to study various docking algorithms and predicting the active site of the molecule. Various docking programs were developed to visualize the 3D structure of the molecule and the docking score can also be analyzed with the aid of different computational methods. Molecular Docking is a structure-based virtual screening (SBVS) that is used to place the computer-generated three-dimensional Structures of small molecules into a target structure in a variety of positions, conformations and orientations. Protein-ligand docking is a new concept with a variety of applications. It acts as a vivacious explore domain because of its significance to structure-based drug design (SBDD), Lead Optimization, Evaluation of Biochemical pathways, in De Novo drug design. In this Review the whole description on Molecular Docking is mentioned here. Through Molecular Docking the Binding mode and affinity of the complex so formed is estimated and thus helps in the Molecular Recognition Process docking towards discovery of new drug leads.

Keywords: Binding Affinity, Computer-Aided Drug Design and Discovery (CADDD), De Novo Drug Design, Lead Optimization, Molecular Docking.

1 INTRODUCTION

The path to drug discovery is a long, challenging & arduous task not to mention the overburdening finances it demands. As of 2014, the average cost of developing a new drug from scratch was found to be an estimated $2.5 billion, an increase of 145% from the previous study done by the same organization in 2003. The major reasons for this drastic increase in the cost is mainly attributed to high failure rate of drugs among others [1] . Understanding of the drug discovery process is important to handle the challenges faced by the pharma companies in terms of cost and innovation. The process of identifying a target, synthesizing an active compound with suitable characteristics like minimal toxicity, high bioavailability, cost-effective synthesis, etc., and finally developing it to introduce in the market is a timeconsuming, extremely complex and risky endeavor [2] . Initially, a target is identified which plays a key role in progress of the disease. Once a link between the target and the disease has been established, the next step is to identify potential candidates which can stop or reverse the progress of the disease [3] . This process starts with the discovery of molecules that show efficacy in a simple screen, called "hits." Screening is a process in which normally a large number of compounds from natural products and online databases are examined for biological activity in high throughput assays. This step in the drug discovery process is very crucial and demands maintaining huge molecular libraries and carrying out thousands or millions of assays, which leaves the academicians and small pharmaceutical companies at a disadvantage and also shoots up the cost for larger industries. Next, the "hits" found are chemically modified to give improved pharmaceutical properties, such compounds are often called "leads." But, it is quite apparent that the method stated above for discovery of a drug has a number of pitfalls. From an academic point of view, carrying out high throughput screens (HTS) is costly, time-consuming and not feasible; while, from an industrial perspective, it does nothing to improve the imminent danger of market saturation.

Truly innovative and blockbuster drugs are what drive the pharmaceutical industry forward but, over the past few years introduction of new molecular entities (NMEs) has vastly reduced. For example, in 2007 only 19 NMEs were approved by the US Food and Drug Administration (FDA), the least since 1983 [4] . Currently, and even in the future it is expected that only slight modifications of the existing blockbuster drugs would be carried out which would further aggravate this problem [5] .

2 FUNDAMENTALS OF MOLECULAR DOCKING

2.1 Definition and basic concept

Molecular docking is a computational method that predicts the preferred binding orientation of a ligand within a target molecule's binding site. The process involves exploring different ligand positions, orientations, and conformations to identify plausible protein–ligand complexes.

The basic concept is that the three-dimensional structures and chemical properties of the protein and ligand influence their interactions. The ligand must adopt a suitable orientation within the binding pocket to establish favourable contacts. Docking algorithms explore possible poses and scoring functions rank them according to estimated interaction quality [1,2] .

2.2 Protein–ligand interactions

Protein–ligand binding is influenced by several types of non-covalent interactions.

1. Hydrogen bonds: These occur between suitable hydrogen-bond donors and acceptors. They can contribute to binding specificity and stability.
2. Hydrophobic interactions: Non-polar portions of the ligand may interact favourably with non-polar regions of the protein binding pocket.
3. Electrostatic interactions: Attraction or repulsion between charged or partially charged groups influences molecular recognition.
4. Van der Waals interactions: These arise from interactions between nearby atoms and depend strongly on their separation.
5. Aromatic interactions: Aromatic rings can participate in interactions such as π–π stacking and cation–π interactions.

The overall binding process also depends on desolations, water molecules, molecular flexibility, and conformational changes. A ligand that forms several favourable interactions may still bind poorly if other energetic factors are unfavourable [6,7].

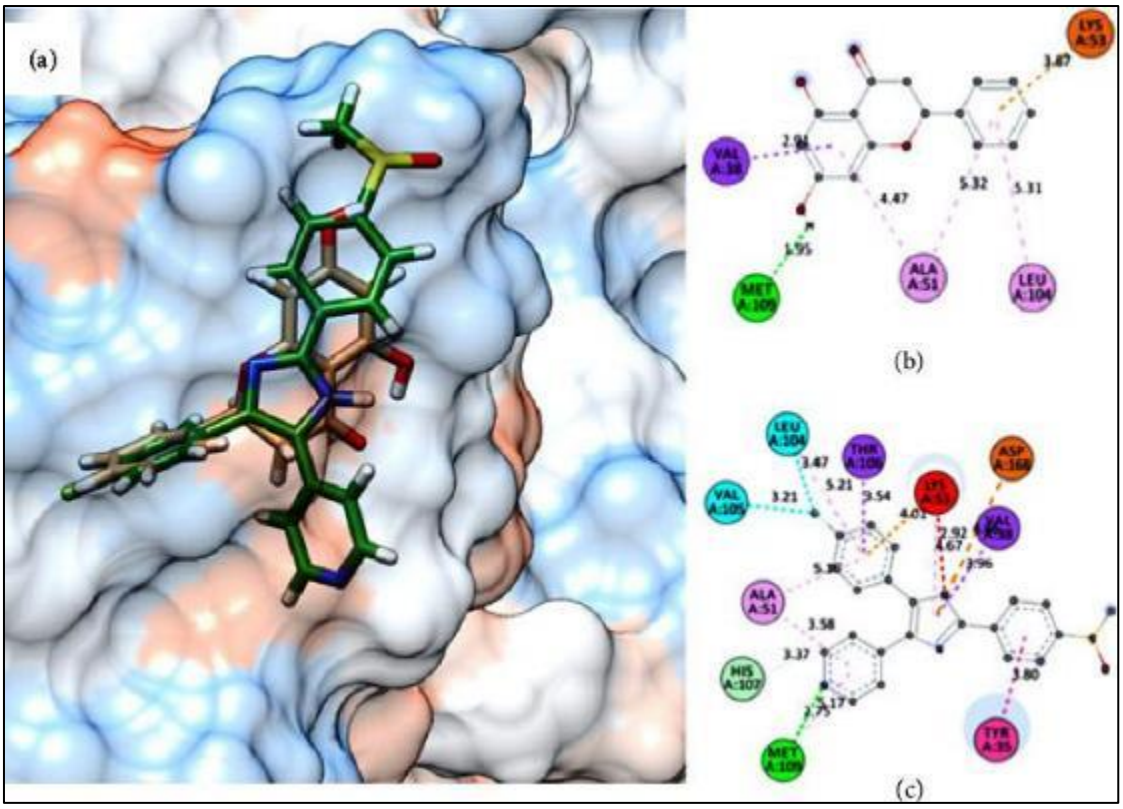


Figure 1: General overview of molecular docking [11]

2.3 Lock-and-key and induced-fit concepts

The lock-and-key model describes a binding site with a shape complementary to its ligand. It is useful for explaining molecular recognition in a simplified manner.

The induced-fit model recognizes that proteins can change their conformations when a ligand binds. This flexibility is important because the binding site may adjust to accommodate the ligand.

Many conventional docking methods treat the protein as rigid or allow only limited flexibility. Consequently, docking predictions may not fully represent the structural changes that occur during actual binding[8,10].

3 TYPES OF MOLECULAR DOCKING

Molecular docking can be classified according to the flexibility of the interacting molecules and the biological partners involved [6,7].

3.1 Rigid docking

In rigid docking, the conformations of both the receptor and ligand are held fixed during the docking process. The algorithm mainly explores their relative position and orientation. This approach is computationally less demanding but cannot fully account for molecular flexibility.

3.2 Flexible docking

Flexible docking allows selected ligand bonds or other molecular degrees of freedom to change during the search. This helps the ligand adopt different conformations within the binding pocket and may improve pose prediction [6,8].

3.3 Semi-flexible docking

Semi-flexible docking generally keeps the receptor rigid while allowing the ligand to change its conformation. This approach is commonly used because it balances computational efficiency with the need to explore ligand flexibility.

3.4 Protein–Ligand Docking

Protein–ligand docking predicts how a small molecule interacts with a protein target. It is widely used to identify potential inhibitors, investigate binding modes, and prioritize compounds for experimental evaluation [6,7].

3.5 Covalent docking

Covalent docking is designed for compounds that form a covalent bond with a target protein. It must account for the geometry and chemistry of the covalent reaction and is particularly relevant to certain enzyme inhibitors. It requires specialized algorithms and assumptions.

Table 1: Types of molecular docking

Type	Main feature	Major limitation
Rigid docking	Both partners are treated as rigid	Limited conformational exploration
Flexible docking	Selected molecular conformations can change	Greater computational cost
Semi-flexible docking	Usually, flexible ligand and rigid receptor	Limited receptor adaptation
Protein–protein docking	Predicts association of two proteins	Large, complex interaction surfaces
Covalent docking	Models covalent ligand attachment	Requires specialized chemical modelling

The choice of docking method depends on the research objective, target structure, ligand characteristics, and available computational resources.

4 MOLECULAR DOCKING WORKFLOW

Molecular docking follows a series of computational steps. Correct preparation and validation are essential because errors introduced early in the process may affect the final results [6,8].

4.1 Selection of the target protein

The first step is to identify a biological target relevant to the disease or biological process being investigated. Suitable targets may include enzymes, receptors, transporters, or other proteins associated with disease mechanisms.

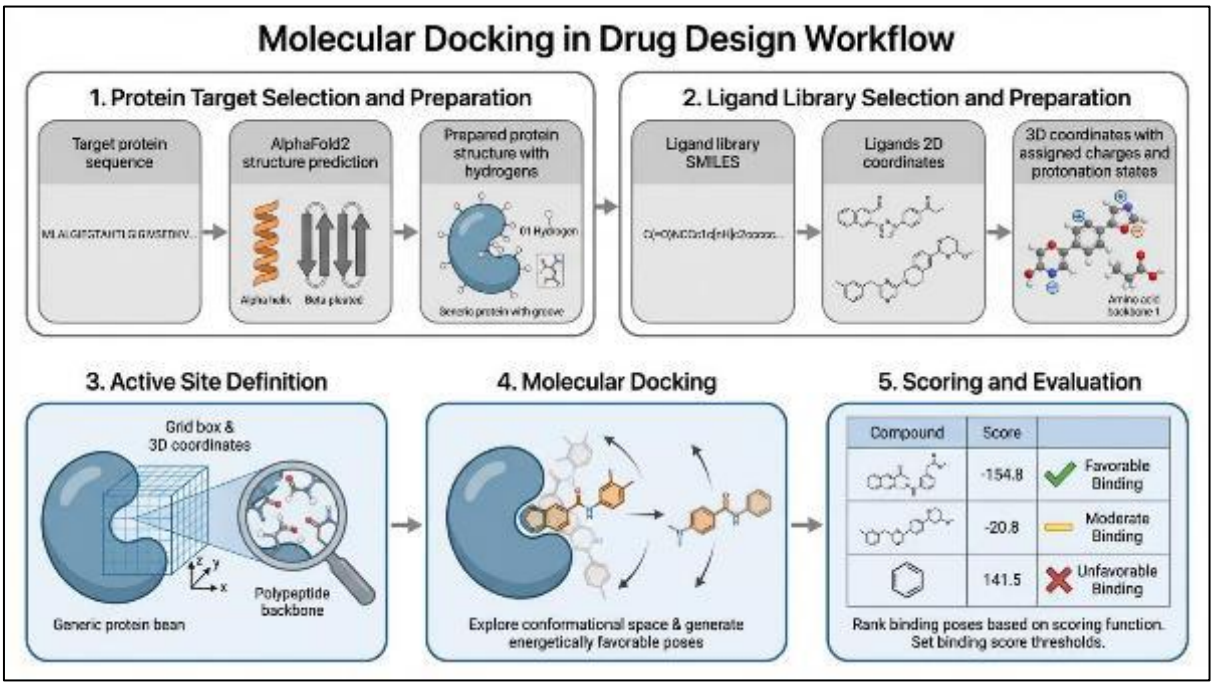


Figure 2: Workflow of molecular docking [17]

Protein structures may be obtained from the Protein Data Bank (PDB), which provides experimentally determined three-dimensional structures. The researcher should check the structure's resolution, completeness, biological relevance, and availability of a suitable binding site [14,15].

4.2 Protein preparation

The downloaded protein structure is prepared before docking. Preparation may involve removing irrelevant molecules, correcting missing atoms or residues where appropriate, adding hydrogens, assigning protonation states, and assigning suitable partial charges.

Water molecules should not be removed automatically in every case. Some conserved waters are important for ligand binding, while others may be unnecessary for a particular docking protocol. Similarly, essential metal ions and cofactors should be retained when they contribute to target structure or activity.

Incorrect protonation states, missing structural information, or inappropriate removal of important molecules can affect docking results [6,7].

4.3 Ligand preparation

The ligand is selected from a chemical database, literature source, or designed compound library. Its structure must be checked for correct connectivity, bond orders, stereochemistry, and ionization state.

The preparation process may involve generating three-dimensional coordinates, adding hydrogen atoms, assigning charges, and exploring relevant conformations [8] . If the ligand can exist in different protonation or tautomeric states, these forms may need to be considered.

4.4 Identification of the binding site

The binding site is the region of the protein where the ligand is expected to interact. It may be identified from a co-crystallized ligand, known active-site residues, experimental evidence, or computational binding-site prediction tools.

When a known ligand is present, its position can help define the docking region. If no binding site is known, blind docking or pocket-prediction methods may be used, although these approaches can be more computationally demanding.

4.5 Docking and pose generation

The docking algorithm explores possible ligand orientations and conformations within the defined region. It searches for poses that fit the binding pocket and satisfy the geometric and chemical requirements of molecular interactions.

Different algorithms use different search strategies. The generated poses are then evaluated by a scoring function to estimate their relative favourability [8,10].

4.6 Scoring and ranking

Scoring functions assign numerical values to predicted binding poses. Depending on the software, scores may approximate intermolecular interaction energy, binding affinity, or a combined empirical estimate.

A more favourable score within the same validated protocol may help prioritize compounds. However, docking scores from different software packages or different targets should not be compared directly without careful justification [10].

4.7 Analysis and validation

The top-ranked poses are examined using molecular visualization tools. Researchers identify hydrogen bonds, hydrophobic contacts, charged interactions, steric clashes, and important amino acid residues.

Validation may include redocking a known ligand into its experimentally determined binding site and comparing the predicted pose with the reference structure. Root-mean-square deviation (RMSD) can be used to measure the difference between corresponding atomic coordinates. An RMSD of approximately 2 Å or less is often used as a practical pose-reproduction benchmark, although interpretation depends on the system and protocol.

Further confirmation may involve molecular dynamics, biochemical assays, or other experimental techniques [6,7,10].

5 MOLECULAR DOCKING SOFTWARE AND TOOLS

Several software packages are used for docking, visualization, and preparation of molecular structures. Their capabilities, licensing, and computational requirements vary [8,9,10].

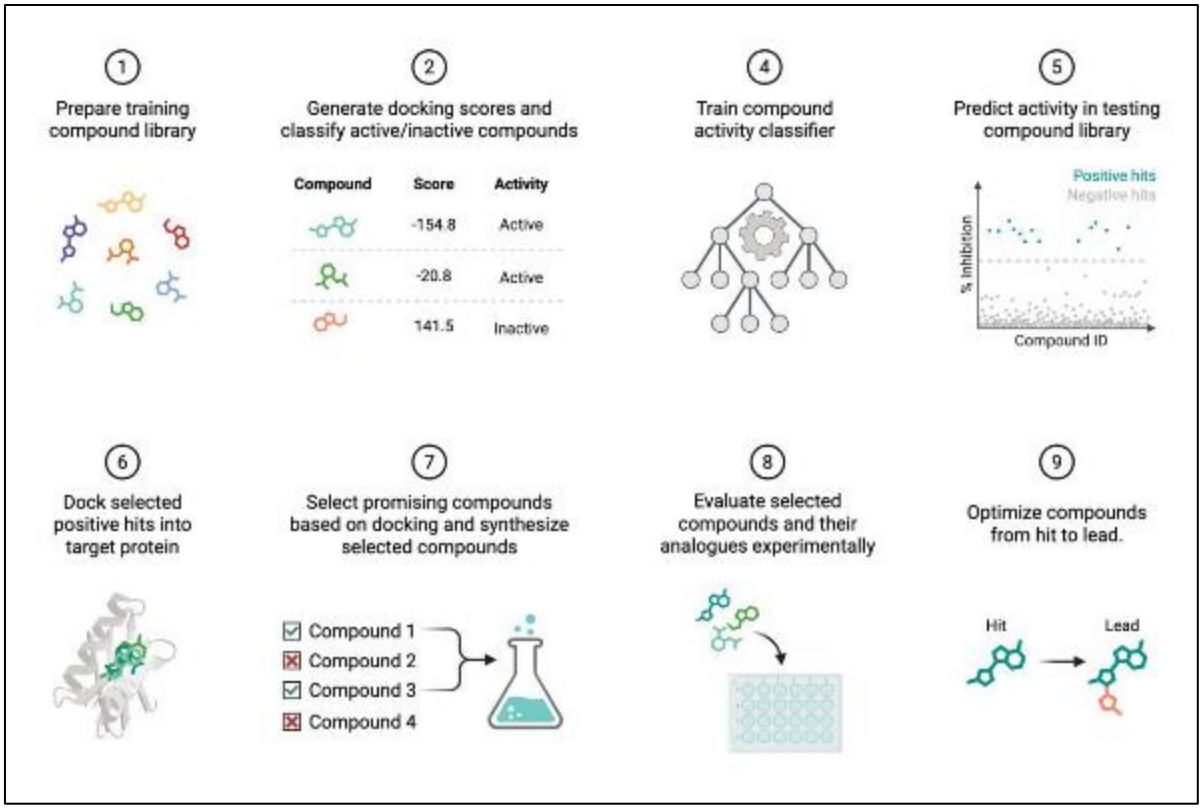


Figure 3: Applications of molecular docking in drug discovery [11]

5.1 AutoDock

AutoDock is a widely used docking program that supports the prediction of ligand binding poses and estimation of interaction energies. It has been applied in numerous academic studies, including the screening of potential inhibitors against biological targets [9].

5.2 AutoDock Vina

AutoDock Vina is a commonly used docking program that combines an efficient search algorithm with a scoring function. It is popular in academic research because it can perform docking with relatively modest computational resources. It is also suitable for virtual-screening workflows [8,12].

5.3 SwissDock

SwissDock is a web-based molecular docking platform designed to support docking studies without requiring every step to be performed locally. Its availability and supported workflows can vary with service updates.

5.4 PyMOL

PyMOL is primarily a molecular visualization tool rather than a docking engine. It can be used to inspect protein structures, view docked complexes, display molecular surfaces, and prepare figures.

5.5 UCSF Chimera and ChimeraX

These programs support the visualization and analysis of molecular structures. They can help researchers examine binding sites, molecular contacts, and structural features of predicted complexes.

5.6 Discovery Studio Visualizer

Discovery Studio Visualizer provides tools for viewing molecular structures and examining protein–ligand interactions. Availability and features depend on the particular product version and licensing arrangements.

Table 2: Comparison of molecular docking software

Tool	Main role	Typical use
AutoDock	Docking and scoring	Pose prediction
AutoDock Vina	Efficient molecular docking	Virtual screening
SwissDock	Web-based docking	Accessible docking studies
PyMOL	Molecular visualization	Structural figures and pose inspection
UCSF ChimeraX	Molecular visualization and analysis	Binding-site examination
Discovery Studio Visualizer	Interaction visualization	Protein–ligand contact analysis

Tool selection should be based on the research objective, software documentation, reproducibility, and availability. A visualization program should not be described as a docking engine unless it actually provides the relevant docking functionality.

6 BINDING AFFINITY AND ANALYSIS OF DOCKING RESULTS

Docking results require careful analysis before conclusions can be drawn about a potential drug candidate [7,10].

6.1 Docking score

A docking score is a numerical estimate used to rank predicted poses or ligands. In many commonly used scoring systems, a more negative score indicates a more favourable predicted interaction. However, the exact meaning and units depend on the software and scoring function.

A docking score is not necessarily an experimentally measured binding free energy. Therefore, it should not be interpreted as definitive evidence that a compound binds strongly.

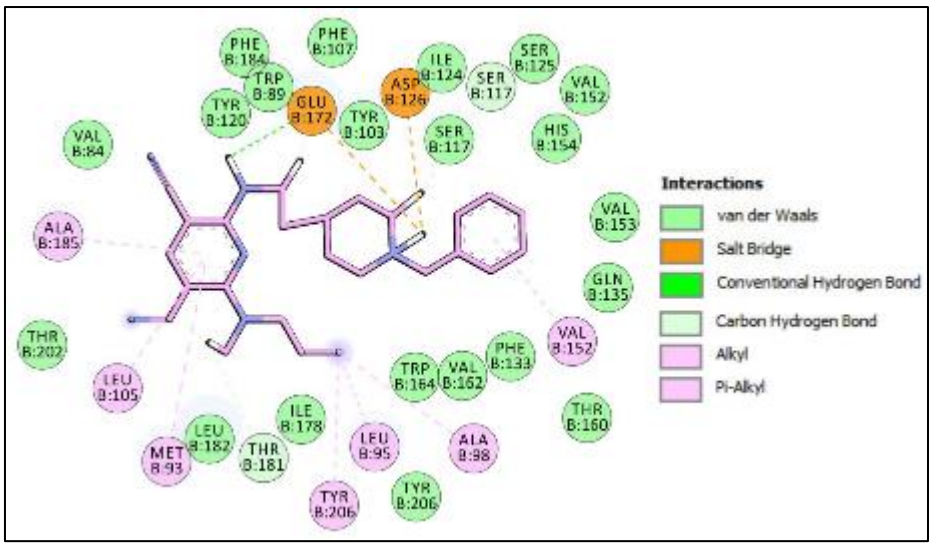


Figure 4: Protein–ligand interaction analysis [18]

6.2 Binding affinity

Binding affinity describes the strength of an interaction between a ligand and a target. Experimental affinity is commonly measured using quantities such as the dissociation constant (K_d) or inhibition constant (K_i), depending on the assay and binding mechanism.

Docking can estimate relative binding favourability, but experimental measurements are required to establish actual affinity. A compound may receive a favourable docking score yet fail to show meaningful inhibition in a biological assay [6,10].

6.3 Hydrogen-bond analysis

Hydrogen bonds can help stabilize a ligand within the binding pocket. Their interpretation involves the distance and geometry between donor and acceptor groups, not just the number of contacts. A large number of predicted hydrogen bonds does not automatically indicate stronger binding [7,10].

6.4 Hydrophobic and electrostatic interactions

Hydrophobic contacts can contribute to ligand accommodation in non-polar pockets. Electrostatic interactions can stabilize or destabilize binding depending on charge distribution and molecular environment. Researchers should also look for steric clashes, unsatisfied polar groups, and unfavourable contacts.

6.5 Amino acid residue analysis

Examining interacting amino acid residues can help explain how a ligand occupies the binding site. Comparison with known active compounds, important catalytic residues, and experimentally characterized binding modes can strengthen the interpretation.

6.6 Validation of docking results

Validation helps determine whether the docking protocol can reproduce known binding behaviour. Redocking a co-crystallized ligand and comparing its pose with the experimental pose is a common method. Cross-docking, comparison with known active and inactive compounds, and prospective experimental testing can provide additional evidence.

The final selection of compounds should consider more than docking scores. Chemical stability, selectivity, solubility, pharmacokinetics, toxicity, and biological activity are also important.

7 APPLICATIONS OF MOLECULAR DOCKING IN DRUG DESIGN AND DISCOVERY

7.1 Virtual screening

Virtual screening involves evaluating large collections of compounds computationally to identify molecules that may bind to a selected target. Molecular docking can rank compounds according to predicted binding poses and scores, allowing researchers to prioritize a smaller number for experimental testing.

Virtual screening can reduce the number of compounds that require laboratory evaluation. Nevertheless, the effectiveness of screening depends on library quality, protein preparation, scoring accuracy, and appropriate validation [6,11].

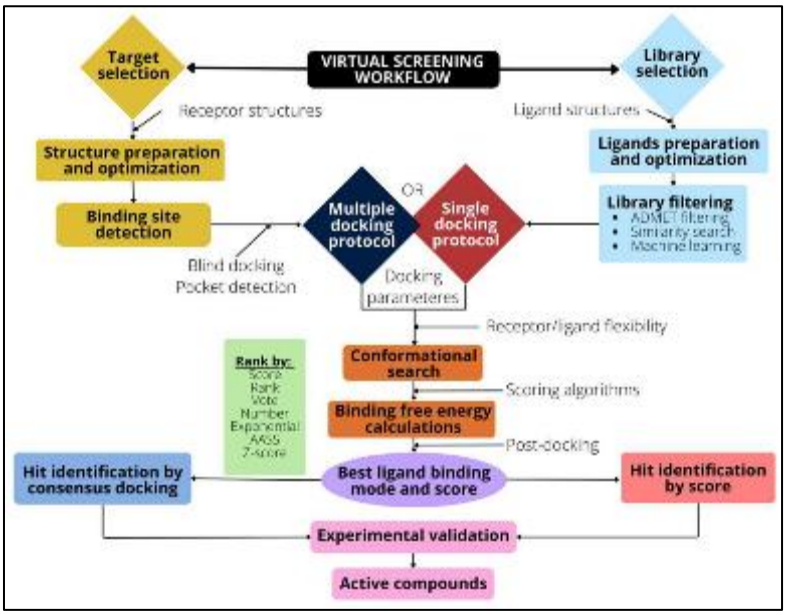


Figure 5: Role of molecular docking in drug discovery [19]

7.2 Structure-based drug design

Structure-based drug design uses the three-dimensional structure of a biological target to guide compound discovery and optimization. Docking helps researchers examine the placement of ligands within binding pockets and identify molecular groups that may improve target interactions.

The structural information can guide the modification of functional groups, the design of new analogues, and the exploration of alternative binding modes. Other computational and experimental approaches are usually needed to assess whether the proposed changes improve biological activity.

7.3 Lead identification and optimization

A lead compound is a molecule that shows promising activity and provides a starting point for further optimization. Docking can help identify possible leads from chemical libraries and support the comparison of related compounds.

During optimization, researchers may modify substituents, ring systems, or functional groups to improve predicted interactions. These changes must also be evaluated for solubility, metabolic stability, selectivity, toxicity, and other drug-like properties [6,11].

7.4 Drug repurposing

Drug repurposing investigates whether an existing medicine may have potential for a different therapeutic indication. Docking can be used to screen known drugs against an additional biological target and identify possible binding interactions.

However, predicted binding alone does not demonstrate clinical usefulness. Drug exposure at the target site, dosing, safety, off-target effects, and experimental evidence must be considered.

7.5 Antiviral drug discovery

Molecular docking has been used to investigate potential inhibitors of viral proteins, including enzymes and other proteins required for viral replication. Researchers can dock candidate compounds into relevant binding sites and study predicted interactions with target residues.

This approach may help prioritize molecules for further antiviral testing. Nevertheless, computational predictions cannot establish antiviral efficacy without experimental evidence, and a compound's ability to inhibit a purified protein may not translate into activity in infected cells.

7.6 Anticancer drug discovery

Docking can support the investigation of compounds targeting proteins involved in tumour growth, cell-cycle regulation, and cancer-associated signalling pathways. It may assist the identification of compounds that could interact with enzymes, receptors, or other relevant targets.

Selectivity is particularly important in cancer research because many targets also perform essential functions in healthy cells. Docking results therefore need to be considered alongside biological activity, toxicity, and effects on normal cells.

7.7 Antibacterial drug discovery

Molecular docking can help investigate compounds that may inhibit bacterial enzymes or proteins involved in cell-wall synthesis, metabolism, and other essential processes. It is useful for exploring possible binding modes and prioritizing candidate inhibitors.

However, bacterial penetration, efflux mechanisms, resistance, and toxicity can affect the actual performance of a compound. These factors require additional computational and experimental investigation.

7.8 Natural-product research

Natural products obtained from plants, microorganisms, and other biological sources are widely investigated for potential therapeutic applications. Docking can be used to examine possible interactions between natural compounds and disease-associated targets.

Before interpreting the results, researchers should verify the identity, stereochemistry, and chemical structures of the selected compounds. Laboratory testing is necessary to confirm the predicted activity.

7.9 Understanding structure–activity relationships

Docking can complement structure–activity relationship (SAR) studies by providing hypotheses about how chemical modifications affect interactions within a binding pocket. Comparing related compounds can help identify structural features that may contribute to predicted binding.

These predictions should be combined with measured biological activity rather than used as a substitute for experimental SAR evidence.

7.10 Contribution to cost and time efficiency

Computational screening can help reduce the number of compounds advanced to more resource-intensive experiments. It may also allow researchers to investigate binding hypotheses before synthesizing new molecules.

However, docking does not eliminate the need for chemical synthesis, laboratory assays, safety testing, or clinical evaluation. Its contribution to efficiency depends on the quality of the computational workflow and how well it is integrated with experimental research.

Table 3: Applications of molecular docking

Application	Role of molecular docking
Antiviral drug discovery	Investigates possible binding to viral protein targets
Anticancer drug discovery	Examines interactions with cancer-associated targets
Antibacterial drug discovery	Identifies potential inhibitors of bacterial proteins
Drug repurposing	Screens existing drugs against alternative targets
Lead optimization	Supports the evaluation of chemical modifications
Natural-product research	Investigates predicted binding of natural compounds

8 RECENT ADVANCES IN MOLECULAR DOCKING

8.1 Artificial intelligence and machine learning

Artificial intelligence (AI) and machine learning (ML) are increasingly being investigated for molecular property prediction, binding-pose prediction, scoring, and compound prioritization. These approaches may identify complex patterns in molecular and structural data that are difficult to capture using conventional scoring functions.

AI-based methods can complement conventional docking, but their performance depends on training data, target similarity, data quality, and validation. Predicted results should not automatically be considered more accurate than established methods [11].

8.2 Integration with virtual screening

Docking is often combined with chemical database searches, pharmacophore filtering, similarity searches, and machine-learning models. This multi-stage approach can remove unsuitable compounds before more computationally demanding calculations are performed.

The resulting candidates are then prioritized for further evaluation. A carefully designed workflow can improve screening efficiency, although overly restrictive filtering may exclude useful compounds.

8.3 Molecular dynamics simulation

Molecular dynamics (MD) simulation studies the movement of atoms over time according to a molecular mechanics model. When used after docking, MD can investigate the stability of a predicted protein–ligand complex, changes in protein conformation, and the behaviour of water molecules.

MD can provide information beyond a single docking pose, but it is computationally more demanding and sensitive to simulation setup, force fields, sampling, and analysis methods. A stable trajectory alone does not prove that a compound has high experimental affinity.

8.4 Improved protein structure prediction

Advances in protein structure prediction have expanded the number of targets for which three-dimensional models may be available. These structures can support target analysis and docking when suitable experimental structures are lacking.

Predicted structures may contain errors, especially in flexible regions or binding pockets. Their suitability for docking should be evaluated rather than assumed [10].

8.5 Integration with QSAR and ADMET

Quantitative structure–activity relationship (QSAR) models estimate biological or chemical properties from molecular descriptors. ADMET prediction examines absorption, distribution, metabolism, excretion, and toxicity-related properties.

Combining docking with QSAR and ADMET analysis can help prioritize candidates based on both predicted target interactions and broader drug-development properties. However, these predictions also require validation and may be unreliable outside the range of the underlying data [16].

9 CHALLENGES AND LIMITATIONS OF MOLECULAR DOCKING

Despite its importance, molecular docking faces several technical and practical limitations.

9.1 Protein flexibility

Proteins are dynamic molecules, and their binding sites may change shape during ligand binding. Treating the protein as completely rigid can prevent docking algorithms from identifying biologically relevant poses. Flexible receptor docking and molecular dynamics can address some aspects of this problem but require additional computational resources [6,7].

9.2 Limitations of scoring functions

Scoring functions simplify complex physical and chemical interactions. They may not accurately account for entropy, solvent effects, protein reorganization, and other contributions to binding free energy. Consequently, the top-ranked ligand may not be the most potent compound experimentally [10] .

9.3 Solvent and water effects

Water molecules can influence binding by forming bridges between the ligand and protein or by competing with ligand interactions. Incorrect treatment of water and desolvation can affect pose selection and scoring.

9.4 Protonation and tautomeric states

Proteins and ligands may exist in different protonation or tautomeric states depending on their chemical environment and pH. Incorrect state assignment can change charges, hydrogen bonding, and predicted binding modes.

9.5 Quality of protein and ligand structures

Missing atoms, incorrect stereochemistry, uncertain side-chain positions, and inaccurate ligand structures can introduce errors. Structure preparation and quality assessment are therefore essential parts of a reproducible docking workflow [7,10].

9.6 Biological activity is not guaranteed

A ligand that fits well into a predicted binding pocket may still fail to show activity because of poor solubility, low permeability, rapid metabolism, toxicity, or insufficient exposure at the target site. Docking does not independently establish efficacy or safety.

9.7 Reproducibility and computational bias

Results can vary with software versions, scoring functions, search parameters, structure preparation, and selected protein conformations. Reproducibility requires documenting the workflow and using suitable validation methods.

Table 4: Challenges and possible solutions

Challenge	Possible improvement
Protein flexibility	Consider multiple receptor conformations
Scoring inaccuracies	Use complementary scoring and validation methods
Solvent effects	Evaluate relevant water molecules and solvation
Incorrect protonation	Check plausible states at relevant pH
Structural errors	Inspect and validate input structures
False-positive predictions	Use experimental assays and appropriate controls
Poor reproducibility	Record software, parameters, structures, and protocols

Future Perspectives

The future of molecular docking will likely involve greater integration with AI, improved structural modelling, more realistic representations of protein flexibility, and better treatment of solvent effects. These developments may improve the prioritization of compounds and support more efficient exploration of chemical space [7,10].

Another important direction is the integration of docking with experimental techniques such as biochemical assays, biophysical binding measurements, structural biology, and cellular testing. Combining computational predictions with experimental data can improve confidence in candidate selection and reveal limitations that cannot be identified through docking alone.

Automated workflows may also improve reproducibility by standardizing protein preparation, ligand processing, docking, scoring, and reporting. Open-source software and freely accessible structural databases can support wider participation in computational drug discovery [6,10,11].

Ultimately, molecular docking is likely to remain an important component of integrated drug discovery. Its greatest value comes from combining structural insight with chemical knowledge, biological evidence, and experimental validation.

10 CONCLUSION

Molecular docking is a valuable computational method for predicting possible interactions between ligands and biological targets. It contributes to virtual screening, structure-based drug design, lead identification, drug repurposing, and the investigation of molecular binding mechanisms. Advances in AI, protein structure prediction, molecular dynamics, and integrated computational workflows continue to expand its potential. Nevertheless, docking scores and predicted poses have limitations and cannot independently establish biological activity, safety, or clinical effectiveness. Careful structure preparation, protocol validation, and experimental confirmation remain essential. When used alongside complementary computational and laboratory techniques, molecular docking can support more systematic and efficient drug design and discovery.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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