# *In-silico* Molecular Docking: Shifting Paradigms in Pesticide Discovery

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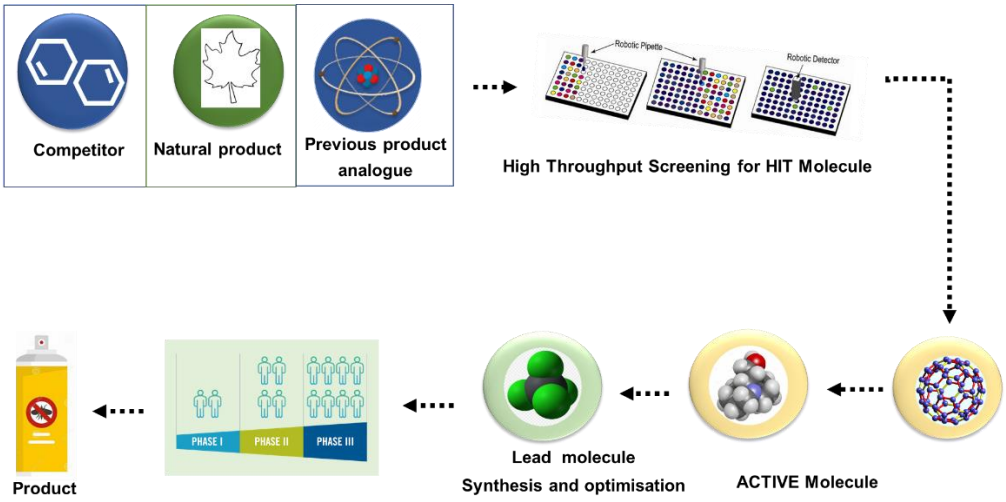
***Abstract*****—** *In-silico molecular docking has emerged as a transformative tool in pesticide discovery, offering detailed insights into the interactions between small molecules and biological targets. This review explores the foundational aspects of molecular docking, outlining its critical steps, including target selection, ligand preparation, docking simulation, scoring and post-docking analysis. It delves into the various types of molecular docking rigid and flexible. The role of molecular docking in insect pest management is examined, highlighting its effectiveness in identifying novel targets, optimizing existing compounds and reducing off-target effects. Furthermore, the diverse applications of molecular docking in pesticide development are discussed, from lead compound identification and structure-based design to resistance management and combination strategies. By leveraging molecular docking, researchers can design more effective and environmentally friendly pesticides, marking a paradigm shift in sustainable pest management practices.*

***Keywords*****— In-silico molecular docking, Pesticide discovery, Insect pest management, Molecular docking applications, Pesticide development, Computational pesticide design, Structure-based drug design, Virtual screening, Lead compound identification, Pesticide resistance.**

## I. INTRODUCTION

Food and nutritional security are of utmost importance for the burgeoning population in the country. On an average 15-20% of potential crop production is lost due to insects, pests, weeds, diseases, nematodes, rodents *etc.*, thus plant protection efforts aim at minimizing crop losses. There are many techniques and technologies for insect-pest control including biological control, transgenic plants, cultural control, mechanical control, physical control and increasingly biopesticides[1], but for many crop-pest-geography scenarios insecticides remain a critical component.

Globally, insects may be destroying an estimated 18-20% of the annual crop production (estimated value=>US$470 billion).[2] Innovation of insect pest control tools has been a critical need for centuries and continues with an expanding global population and the longstanding threats from insect and insect-borne diseases[3]. Amongst different measures, chemicals quickly gained great popularity as an efficient, labour-saving and economic tool in pest management in most agricultural sectors.[4] In other words, the most frequent method of managing pests and diseases in most agricultural sectors is through the application of pesticides.[5]




Strategic resources like pesticides are essential to the security of the country's food supply. Global figures show that after using pesticides, 35% of cash crops are lost annually; if pesticides are discontinued, this loss climbs to 70%.[6] In addition to saving labor, lowering the price of agricultural products and increasing economic efficiency, the use of pesticides is crucial for several processes related to plant growth, regulation, harvesting, storage, transportation and processing.[7] The efficacy of pesticide development has risen significantly with the adoption of computer technologies.[8-9] One of the most representative computer techniques, molecular docking technology, can improve our capacity to address issues like pesticide molecular target identification, pesticide molecular design, pesticide resistance prediction, toxicological analysis and environmental safety risk assessment.[10-14]

During the early stages of pesticide creation, traditional methods such as similar synthesis, random screening and natural active agent simulation played a significant role.[15-18] For example, the herbicides alachlor[19], nitrofen[20] and triadimefon[21] were discovered as pesticides by random screening approaches. However, the limitations of using traditional methods to create pesticides are high blindness, low success rates, and prolonged development cycles, all of which severely restrict the amount of research and development that can be done on pesticides.

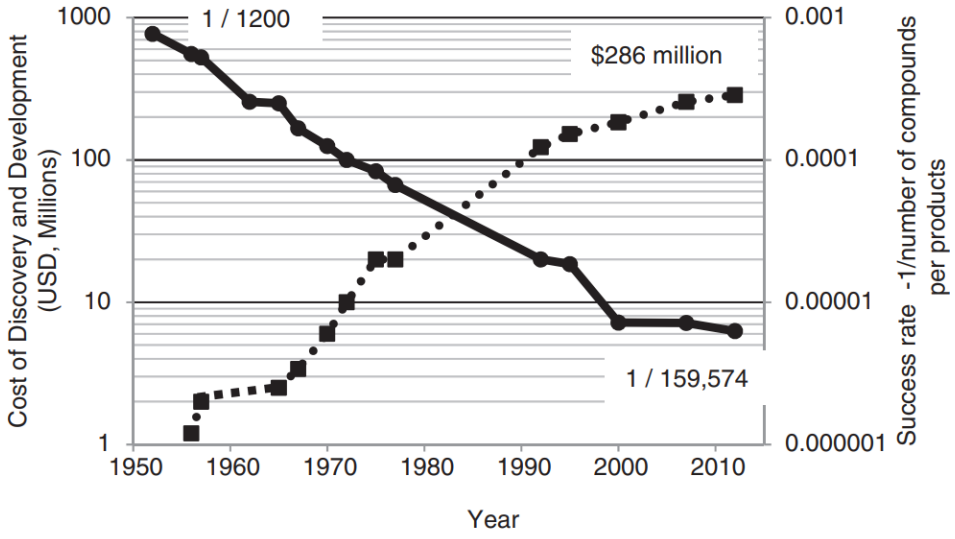



**FIGURE 1: Cost of agrochemical development (dashed line) versus screening success (solid line)**

Screening success ratio=1/number of compounds that need to be screened for each product found. Data adapted, in part, from other studies.[22]

The effective development of a new pesticide necessitates the synthesis and screening of over 159,000 chemicals at a cost of about $286 million, with an average period of 11.5 years from first synthesis to market introduction, according to internationally accepted statistics.[22] Additionally, weed and pest resistance are becoming exacerbated due to increased chemical

use. The creation of new chemical pesticides is vital because of the need to solve important issues including pesticide residues and the harmful effects of pesticides on non-target organisms.[23-34]

One of the key instruments for pesticide research and development, virtual screening technology with molecular docking at its core can compensate for the lack of traditional pesticide creation methods by substantially raising the screening success rate for pesticide lead compounds. For instance, Vaidya and associates[35] screened the abscisic acid receptor agonist Opabactin from the ZINC database using the GLIDE docking approach. Another significant use of molecular docking is reverse docking, which is useful for screening chemicals for possible targets for protein pesticides. To some extent, the toxicity of pesticides can be mitigated in the early stages of pesticide production by using reverse docking to identify probable targets of first-to-compound chemicals. By examining the interaction between small-molecule ligands and receptor biomolecules, a theoretical technique called molecular docking is utilized to investigate the interaction between proteins and ligands. It can predict the binding mechanism and affinity strength.[36-38]

Thus, molecular docking has also been applied to the study of pesticide resistance mechanisms and the environmental detection of pesticides and their metabolites[39-41]. Molecular docking has investigated the use of several machine learning (ML) techniques within the past decade[42-43]. The most common method entails creating scoring functions to estimate a protein-ligand complex's binding affinity. These estimations are then applied to separate various chemicals and binding positions to identify genuine binders and estimate their binding mode. Because molecules are naturally represented as graphs (a collection of nodes or atoms connected by edges or bonds), a deep neural network-based method called deep graph learning can learn from graph-structured data-has been used more and more in this research.[44-45]

A so-called deep docking approach was recently proposed by Gentile *et al.*[46] to expedite the virtual screening of large databases. This deep learning model uses docking and is based on a multilayer feed-forward neural network. Its goal is to correlate molecular fingerprints with docking scores of molecules. With the help of this technique, Tang *et al.*[47] were able to speed up docking-based virtual screening and find a novel A2AR antagonist for extremely large molecular libraries. Tang *et al.*[47] found a novel A2AR antagonist for enormous chemical libraries by using this strategy to speed up docking-based virtual screening.

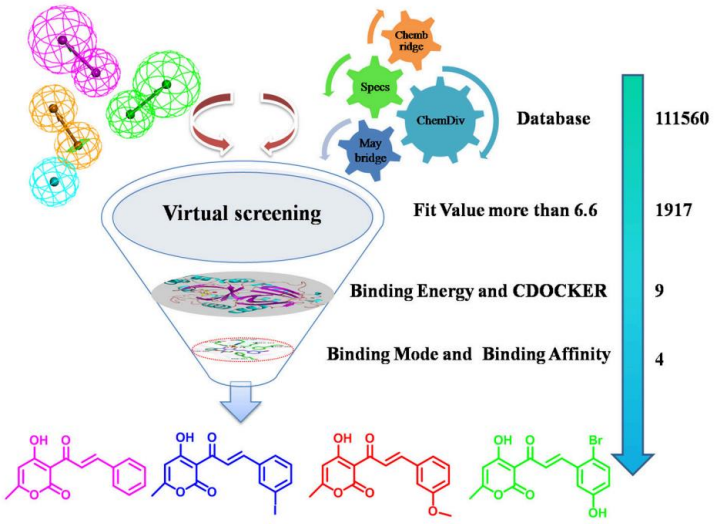



**FIGURE 2: Workflow of virtual screening for different compounds adapted from other studies[48]**

Molecular docking technology has emerged as a powerful and increasingly popular tool in pesticide development. However, alongside its numerous advantages, it also has certain limitations. These drawbacks are highlighted in various pesticide research articles; for instance, Chen encountered difficulties in obtaining virtual screening results using a single screening method.[49] Additionally, the molecular docking program itself has inherent issues, such as the flexibility of the target protein and the accuracy of the scoring function. Although there have been significant advancements in improving the scoring function, accurately and quickly predicting receptor-ligand interactions continues to be a major challenge.[50-51]

Therefore, although docking experiments have made valuable contributions to our understanding of target-ligand interactions in drug discovery projects, their results should be viewed as preliminary and as a foundation for more comprehensive and accurate analyses.[52] This article reviews the fundamental principles of molecular docking, available docking software, and pesticide-related databases, along with the challenges associated with molecular docking. We provide a summary of how this

method is applied in pesticide development, discuss the issues encountered in its use, and explore the prospects for molecular docking in the field of pesticides. Additionally, we aim to offer a theoretical basis to support the development and application of new pesticides.

## II. PRINCIPLE OF MOLECULAR DOCKING

Molecular docking is a widely used computational technique for examining how small molecules bind to receptors. The core concept of molecular docking involves assessing the binding strength of these small molecules by positioning them within the active site of the receptor. This process relies on geometric, energetic, and chemical complementarity to determine the most favorable binding mode.[52-57] This approach is rooted in Emil Fischer's "lock-and-key model," which postulates that enzymes and substrates have precisely complementary structures, similar to a key fitting into a lock, with both the enzyme and substrate being rigid and unchanging.[58]

However, as research has progressed, experimental data have increasingly shown that the conformations of both receptors and small molecules are not static during binding. Instead, the concept of "induced fit," proposed by Koshland, has gained prominence.[59-63] This theory posits that the binding interaction is dynamic, with the receptor adapting its conformation in response to the presence of the small molecule. Consequently, the receptor and small molecule undergo mutual adjustments to achieve an optimal complementary fit.[64]

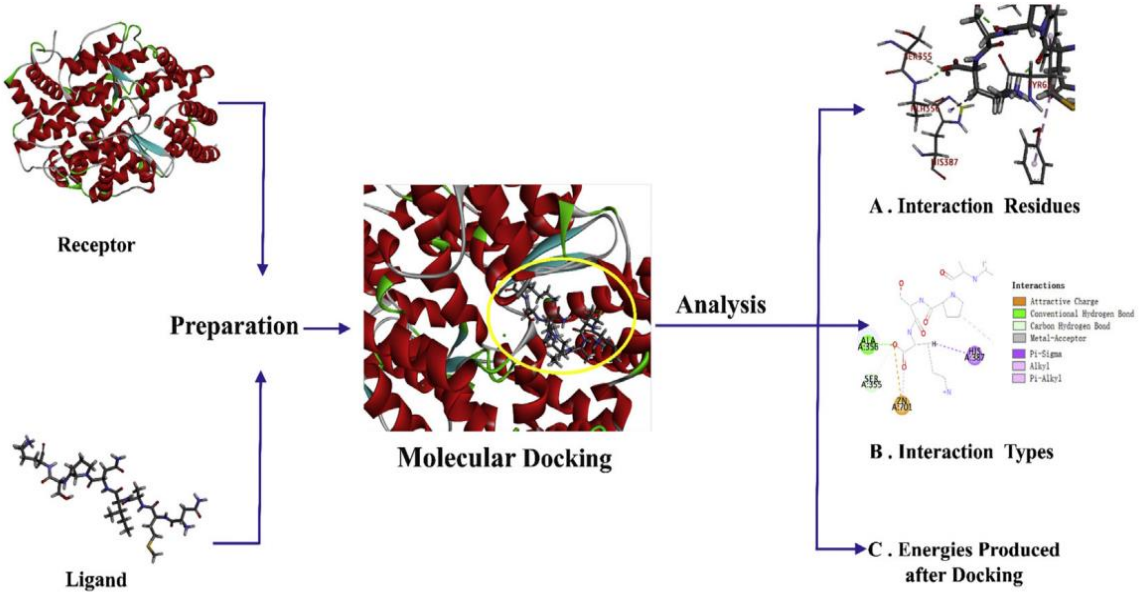



**FIGURE 3: General procedures for molecular docking adapted from other studies[65]**

## III. STEPS OF MOLECULAR DOCKING:

### 3.1 Retrieval and preparation of target receptor structure:

The retrieval and preparation of the target receptor structure are crucial initial steps in molecular docking, as the quality of the receptor model directly impacts the accuracy of the docking results. In molecular docking, the target receptor structure serves as the binding site for ligands and influences the accuracy of docking predictions. Retrieving and preparing this structure involve accessing relevant databases, resolving structural issues and optimizing the receptor for docking simulations.

- **Accuracy:** The quality of the receptor structure directly impacts the reliability of docking results.66
- **Specificity:** Proper preparation ensures that the receptor reflects the biological environment accurately, allowing for specific ligand-receptor interactions 67.
- **Compatibility:** Preparing the receptor structure involves addressing issues such as missing atoms, water molecules and other heteroatoms, ensuring compatibility with docking software.68

#### 3.1.1 Retrieval of Target Receptor Structure:

**1) Identify the Receptor:**

Determine the biological target of interest (e.g., a protein, enzyme, or receptor) relevant to the study.

**2) Access Structural Databases:**

Retrieve the 3D structure of the receptor from structural databases such as the Protein Data Bank (PDB) (http://www.rcsb.org/). The PDB is a comprehensive resource containing experimentally determined structures of proteins, nucleic acids and complex assemblies.[69]

### 3.1.2 Selection Criteria:

Choose the appropriate structure based on resolution, completeness, and relevance. High-resolution X-ray crystallography or NMR structures are preferable.

If multiple structures are available, select the one that best represents the biologically active conformation or the one with a co-crystallized ligand if available.

### 3.1.3 Preparation of Target Receptor Structure:

**A) Remove Unnecessary Molecules:**

- **Water Molecules:** Remove crystallographic water molecules unless they are known to play a critical role in ligand binding.
- **Ligands and Ions:** Remove any bound ligands, ions, or other small molecules that are not part of the binding site unless they are essential for receptor stability.

**B) Add Hydrogen Atoms:**

Hydrogen atoms are typically not resolved in X-ray crystallography. Add hydrogen atoms to the receptor structure to ensure proper hydrogen bonding and electrostatic interactions during docking.

**C) Assign Atomic Charges:**

Assign appropriate atomic charges to the receptor atoms. The choice of charge model (e.g., AMBER, CHARMM) can affect the docking results.

**D) Check for Missing Residues and Atoms:**

Identify and rebuild any missing residues or atoms using homology modeling tools or software like Modeller or Swiss-Model.

**E) Optimize the Geometry:**

Optimize the geometry of the receptor, especially the side chains in the binding site, to relieve any steric clashes and ensure a realistic conformation.

**F) Define the Binding Site:**

Identify and define the binding site or active site. This can be based on the known binding location of co-crystallized ligands or predicted using binding site prediction tools.

**G) Energy Minimization:**

Perform an energy minimization of the receptor structure to relax the conformation and eliminate any residual strain or unrealistic geometries introduced during preparation steps.70

### 3.1.4 Validate the Prepared Structure:

Validate the prepared structure by checking for proper geometry, bond lengths, bond angles and overall structural integrity using validation tools.[71]

### 3.1.5 Tools and Software

- **Molecular Visualization:** PyMOL, Chimera
- **Preparation and Optimization:** AutoDockTools, Maestro (Schrödinger), MOE (Chemical Computing Group)
- **Homology Modeling:** SWISS-MODEL, Modeller
- **Charge Assignment:** AMBER, CHARMM, GROMACS

By carefully retrieving and preparing the target receptor structure, you ensure a robust foundation for subsequent docking studies, leading to more accurate and reliable predictions of ligand binding

### 3.2 Retrieval and preparation of target ligand structure:

Ligands can be obtained from various databases like ZINC or PubChem. The retrieval and preparation of the ligand structure are essential steps in molecular docking, as the ligand's quality affects the docking accuracy and the predicted binding mode.[72]

#### 3.2.1 Retrieval of Target Ligand Structure

**A) Identify the Ligand:**

Determine the small molecule or ligand of interest that will be docked to the receptor.

**B) Access Structural Databases:**

Retrieve the 3D structure of the ligand from chemical databases such as:

PubChem (https://pubchem.ncbi.nlm.nih.gov/)

ChEMBL (https://www.ebi.ac.uk/chembl/)

ZINC (http://zinc.docking.org/)

DrugBank (https://www.drugbank.ca/)

**C) Input Ligand Information:**

If the ligand is not available in these databases, draw the chemical structure using molecular drawing tools like ChemDraw or MarvinSketch, and generate a 3D model using conversion tools.

#### 3.2.2 Preparation of Target Ligand Structure:

**A) Generate the 3D Structure:**

If starting from a 2D structure, use tools like Open Babel or the ligand preparation functionalities in software like Maestro (Schrödinger) or MOE to convert the 2D structure to a 3D conformation.

**B) Assign Proper Protonation States:**

Determine and assign the correct protonation state of the ligand, considering the pH of the biological environment. Tools like Epik (Schrödinger) or Protonate3D (MOE) can predict the most likely protonation states.

**C) Add Hydrogen Atoms:**

Add all hydrogen atoms to the ligand, including polar hydrogens. This step is crucial for accurate interaction predictions.

**D) Assign Partial Atomic Charges:**

Assign appropriate partial atomic charges to the ligand atoms. This can be done using quantum chemistry methods (e.g., AM1-BCC in Antechamber) or force field-based methods (e.g., Gasteiger charges).

**E) Energy Minimization:**

Perform an energy minimization of the ligand to optimize its geometry. This step helps in relieving any steric clashes and ensures a stable conformation. Software like Avogadro, MMFF94 force field in Open Babel, or the minimization tools in Maestro or MOE can be used.

**F) Generate Multiple Conformations (Optional):**

To account for ligand flexibility, generate multiple conformations or tautomers of the ligand using tools like Omega (OpenEye) or LigPrep (Schrödinger).73

#### 3.2.3 Validate the Ligand Structure:

Verify the prepared ligand structure by checking for correct geometry, bond lengths, bond angles and the absence of any unrealistic features.

#### 3.2.4 Tools and Software

- **Molecular Drawing:** ChemDraw, MarvinSketch
- **3D Structure Generation:** Open Babel, Avogadro

**Protonation State Prediction:** Epik (Schrödinger), Protonate3D (MOE)

Charge Assignment: Antechamber (AMBER), Gasteiger charges

**Energy Minimization**: Avogadro, MMFF94 in Open Babel, Maestro (Schrödinger), MOE

Conformation Generation: Omega (OpenEye), LigPrep (Schrödinger)

### 3.3 Docking:

The ligand is docked onto the receptors and the interactions are checked in available docking tools like AutoDock, SwissDock, GOLD, Sanjeevini, *etc.*

## IV. PHYSICOCHEMICAL PROPERTIES PREDICTION:

In molecular docking, predicting the physicochemical properties of ligands and receptors is crucial for understanding their behavior in biological systems and optimizing ligand binding. These properties provide insights into the ligand's potential bioavailability, stability and interaction profiles. Here are the key physicochemical properties considered in molecular docking and how they are predicted:

### 4.1 Molecular Weight (MW)

Importance: Influences the ligand's ability to permeate cell membranes and its overall drug-likeness.

Prediction: Calculated as the sum of the atomic weights of all atoms in the molecule. Tools like ChemDraw, Open Babel, and various cheminformatics software can compute MW easily.[74]

### 4.2 LogP (Partition Coefficient)

Importance: Indicates the lipophilicity of a compound, affecting its solubility and permeability.

Prediction: Calculated using software like ChemDraw, ALOGPS, and MarvinSketch. It estimates the ratio of concentrations of a compound in a mixture of two immiscible solvents (usually octanol and water).[75]

### 4.3 Topological Polar Surface Area (TPSA)

Importance: Correlates with the drug's ability to be absorbed by the human body, including oral bioavailability and blood-brain barrier penetration.

Prediction: Calculated based on the surface areas of polar atoms (usually oxygen and nitrogen) using tools like ChemAxon, SwissADME, and RDKit.[76]

### 4.4 Hydrogen Bond Donors and Acceptors

Importance: Essential for predicting the interaction strength between the ligand and the receptor.

Prediction: Counted directly from the molecular structure. Software like MarvinSketch and Open Babel can provide these counts.[77]

### 4.5 Rotatable Bonds

Importance: Affects the molecule's flexibility and conformational entropy, influencing binding affinity and specificity.

Prediction: Calculated by identifying the number of single non-ring bonds attached to non-terminal heavy atoms. Tools like RDKit and ChemAxon provide this information.

### 4.6 Molecular Volume and Surface Area

**Importance:** Relevant for understanding steric interactions within the binding site and predicting pharmacokinetic properties.

**Prediction:** Tools like PyMOL, Chimera, and molecular modeling software can calculate these parameters using 3D structures.

### 4.7 pKa (Acid Dissociation Constant)

Importance: Influences the ionization state of a molecule at a given pH, affecting solubility, permeability, and binding interactions.

Prediction: Estimated using cheminformatics tools like MarvinSketch and ACD/Labs, which provide pKa values for different ionizable groups in the molecule.[78]

### 4.8 Electrostatic Properties

Importance: Determines the strength and orientation of electrostatic interactions between the ligand and the receptor.

Prediction: Calculated using quantum mechanical methods (e.g., Gaussian) or empirical methods (e.g., AM1-BCC, Gasteiger charges). Tools like AutodockTools can assign partial charges to atoms.

### 4.9 Solubility (LogS)

Importance: Affects the compound's bioavailability and formulation.

Prediction: Estimated using QSAR models and software like ChemAxon and ADMET Predictor.[79]

### 4.10 Bioavailability and Drug-likeness

Importance: Overall assessment of the compound's potential as a drug based on multiple physicochemical properties.

Prediction: Tools like SwissADME, MolSoft, and Lipinski's Rule of Five check compliance with key drug-likeness criteria.

### 4.11 Tools and Software for Physicochemical Properties Prediction

- **ChemDraw:** For drawing chemical structures and calculating basic properties like MW, LogP, and hydrogen bond donors/acceptors.
- **MarvinSketch:** Comprehensive tool for calculating pKa, LogP, TPSA, and other properties.
- **SwissADME:** Web-based tool that provides extensive ADME (absorption, distribution, metabolism, and excretion) predictions, including physicochemical properties.
- **RDKit:** Open-source cheminformatics toolkit for Python that can calculate various molecular descriptors.
- **PyMOL and Chimera:** Molecular visualization tools that can also calculate surface area and volume.
- **ADMET Predictor:** For predicting ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, including solubility and bioavailability.
- **Open Babel:** Open-source tool for converting chemical file formats and calculating basic properties.
- **ACD/Labs:** Comprehensive suite for predicting a wide range of physicochemical properties including pKa and solubility

**A) Scoring function:** The scoring function's goal is to quickly distinguish between correct and incorrect poses, or between binders and inactive substances. Scoring functions, on the other hand, require making several assumptions and simplifications while predicting the binding affinity between the ligand and protein rather than computing it. There are three types of scoring functions: force-field-based, empirical-based, knowledge-based and consensus scoring.[80]

**B) Force Field-Based Scoring Functions:** These estimate the binding energy of a protein-ligand complex by summing contributions from bond terms (bond stretching, angular bending, and dihedral changes) and non-bond terms (electrostatic and van der Waals forces). The calculations rely on classical mechanics equations to determine the energy associated with each term. A major limitation is that they do not account for solvation effects, where polar groups prefer aqueous environments and non-polar groups prefer non-aqueous environments.[81]

**C) Empirical-Based Scoring Functions:** These evaluate the binding energy of a protein-ligand complex by summing a set of weighted empirical energy terms, including van der Waals forces, hydrogen bond energy, electrostatic energy, entropy, desolvation, and hydrophobic forces. They are generally more computationally efficient compared to other scoring functions due to the simplicity of their energy terms.[81]

**D) Knowledge-Based Scoring Functions:** These derive the binding energy of protein-ligand complexes by analyzing structural information from known protein-ligand complexes. Their main advantage is computational simplicity, which enhances the efficiency of screening large compound databases.[81]

**E) Consensus Scoring:** This approach aims to improve scoring accuracy by combining multiple scoring functions to balance out the errors inherent in individual scoring methods. This trend has emerged due to the imperfections present in each type of scoring function.[81]

**F) Molecular dynamics simulations:** Molecular dynamics (MD) simulations are integral to modern molecular docking studies, offering dynamic insights into ligand-receptor interactions that static docking alone cannot provide. MD simulations are widely used in conjunction with molecular docking to refine docking results, explore the flexibility of molecular systems, and gain deeper insights into the dynamic behavior of ligand-receptor interactions.

## V. IMPORTANCE IN MOLECULAR DOCKING

- **Capturing Flexibility:** MD simulations account for the flexibility of both ligands and receptors, overcoming the limitations of rigid-body docking. This results in more accurate predictions of binding modes and affinities.[82]
- **Refining Docking Results:** MD simulations refine initial docking poses by allowing the system to relax and adopt more favorable conformations.[83]
- **Evaluating Stability:** They help assess the stability of the ligand-receptor complex, identifying stable binding poses and providing insights into binding kinetics.[84]
- **Exploring Binding Pathways:** MD simulations elucidate binding and unbinding pathways, crucial for designing better ligands.[85]

### 5.1 Workflow:

- **Initial Docking:** Perform molecular docking to generate initial ligand poses within the receptor's binding site using software like AutoDock, AutoDock Vina, or Glide (Morris et al., 2009; Trott & Olson, 2010).
- **System Preparation:** Select the best-scoring poses, solvate the system, add counter-ions, and perform energy minimization to remove steric clashes.[86]
- **Molecular Dynamics Simulation**: Conduct MD simulations using GROMACS, AMBER, or CHARMM. Typical simulations include equilibration (NVT and NPT ensembles) followed by production runs to observe the system's dynamics.[87-88] Monitor key parameters such as RMSD, RMSF, hydrogen bonds, and interaction energies to assess complex stability.[89]
- **Post-Simulation Analysis:** Analyze trajectories to evaluate the stability and behavior of the ligand-receptor complex, focusing on conformational changes, binding interactions, and complex stability.[90]

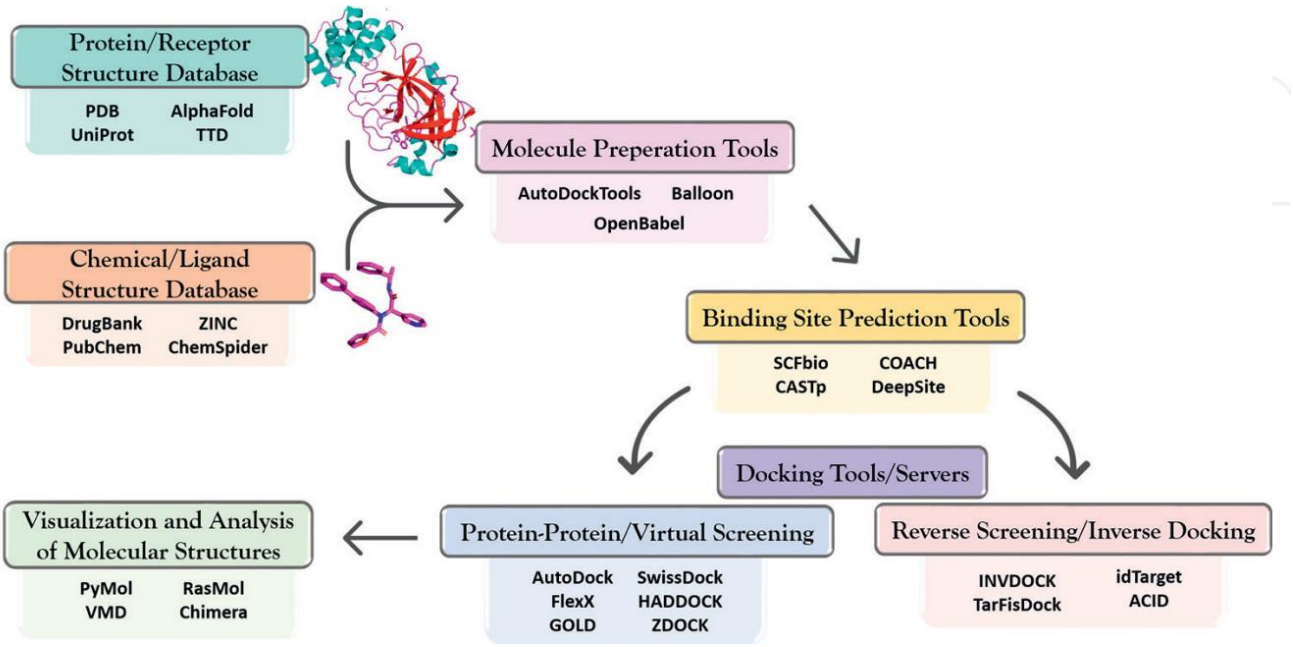
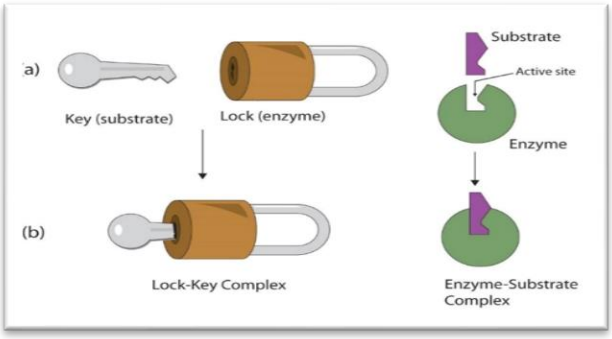


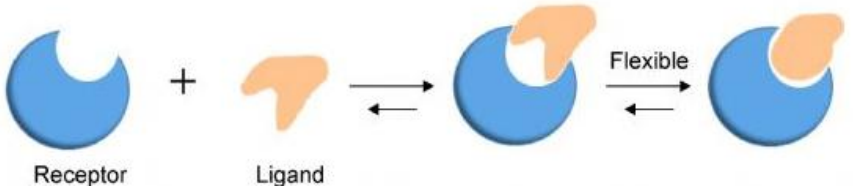

**FIGURE 4: The procedures that can be followed and the tools that can be used before, during and after protein-ligand molecular docking in drug design[91]**

### 5.2 Types of molecular docking

**(1) Rigid docking:** It treats both the receptor and ligand molecules as conformationally rigid. It searches for rigid body transformations that best fit the ligand into the receptor.[92]




**(2) Flexible docking:** Flexible ligand docking treats the ligand as a conformationally flexible molecule, by searching over both ligand conformations and rigid body transformations to identify the best fit of the ligand in the receptor, which is treated as a rigid body.[93]




### 5.3 Role of molecular docking in insect-pest management:

*In-silico* molecular docking analysis of the fusion protein (Vip3Aa-Cry1Ac) against aminopeptidase-N (APN) and cadherin receptors of five Lepidopteran insects (*Agrotis ipsilon, Helicoverpa armigera, Pectinophora gossypiella, Spodoptera exigua, and S. litura*) revealed that the Ser290, Ser293, Leu337, Thr340, and Arg437 residues of the fusion protein are involved in the interaction with insect receptors. The *H. armigera* cadherin receptor, however, showed no interaction which might be due to either loss or burial of interactive residues. These findings revealed that the Vip3Aa-Cry1Ac fusion protein has a strong affinity against Lepidopteran insect receptors and hence has the potential to be an efficient broad-range insecticidal protein (Ahmad *et al*., 2015).[94] The molecular docking of 30 polyphenolic compounds of *Rosa canina* L. against the acetylcholinesterase enzyme of the cereal pest *Rhopalosiphum padi* has highlighted seven important substances based on the binding energies, which were significantly lower than that of the commercial insecticide malathion. Seven components showed intense links with the catalytic site residues of the enzyme, indicating high inhibitory potential of *R. canina's* polyphenolic compounds against the *R. padi* (Benslama *et al*., 2021).[95] Gurbuz-Colak (2023)[96] screened 3,150 natural compounds against the ryanodine receptor of Diamondback moths. Of the 28 compounds selected based on binding energies (threshold of -6.0 kcal/mol) using AutoDock Vina, three natural compounds *viz*., dorsmanin B, chartaceone B, and 7-O-galloyltricetifavan, demonstrated as potential pesticide candidates against Diamondback moth. Rodrigues *et al*. (2021)[97] develop computer-assisted predictions for Lamiaceae family compounds against *Aphis gossypii* and *Drosophila melanogaster* for their insecticidal activity. Structure analysis revealed ent-kaurane, kaurene and clerodane diterpenes as the most active, showing excellent results. They also found that the interactions formed by these compounds were more stable, or presented similar stability to the commercialized insecticides tested. Overall, they concluded that the compounds bistenuifolin L (1836) and bistenuifolin K (1931), were potentially active against *A. gossypii* enzymes; and salvisplendin C (1086) and salvixalapadiene (1195), are potentially active against *D. melanogaster*. They observed and highlight that the diterpenes bistenuifolin L (1836), bistenuifolin K (1931), salvisplendin C (1086) and salvixalapadiene (1195), present a high probability of activity and low toxicity against the species studied. Khanna *et al*. (2023)[98] study *in-silico* docking to evaluate the interaction of various triterpenoids present in neem with the ecdysone receptor of two economically important lepidopteran pests *viz*., *Helicoverpa armigera* (HaEcR) and *Plutella xylostella* (PxEcR). Twenty triterpenoids were selected for the study, and their docking scores with HaEcR and PxEcR were calculated using the program AutoDock Vina. A commercially available DAH insecticide, tebufenozide, was used as a reference ligand. Out of the twenty triterpenoids used for the study, six and nine triterpenoids recorded binding energy lower than the reference ligand, tebufenozide, when docked with HaEcR and PxEcR, respectively. Four triterpenoids, viz., isomeldenin, azdiradione, 6-deacetylnimbinene, and nimocinol, docked effectively with the ecdysone receptor of both insect pests. Triterpenoids such as tirucallol, 3-tigloylazadirachtol and azadirone, although recorded binding energy lower than tebufenozide when docked with PxEcR. The lower binding energy of the lead compounds suggests their stable interaction with

the receptor molecule and their possible use as an ecdysone agonist or antagonist for effective insect control. Nakao *et al*. (2013)[99] revealed effect of meta-diamide and NCAs (non-competitive antagonist) on mutant Drosophila RDL GABA receptors expressed in Drosophila Mel-2 cells. They observed NCAs had little or no inhibitory activity against at least one of the three mutant receptors (A2' S, A2' G, and A2' N), which were reported to confer resistance to NCAs. In contrast, meta-diamide 7 inhibited all three A2' mutant receptors, at levels comparable to its activity with the wild-type receptor. Molecular modeling studies also suggested that the binding site of meta-diamides was different from those of NCAs. Meta-diamide insecticides are expected to be prominent insecticides effective against A2' mutant RDL GABA receptors with a different mode of action.

## VI. CONCLUSION

The problem of environmental and health toxicity of a large number of conventional chemical insecticides, besides uprising scenarios resistant insects to these chemicals are becoming increasingly ineffective for the control of crop pests, pushing researchers to a continuous search for new effective products. *In-silico* molecular docking in the realm of pesticide discovery is marking a significant departure from traditional methods. Through computational modeling and virtual screening, researchers can navigate the vast chemical space with unprecedented speed and precision, revolutionizing the way we identify and optimize pesticides. The paradigm shift towards *in-silico* approaches heralds a new era of efficiency and sustainability in agriculture. By harnessing the power of computational algorithms and molecular simulations, scientists can rapidly predict the binding affinity of pesticide compounds to target receptors, accelerating the drug discovery process manifold. This not only expedites the development of novel pesticides but also minimizes the reliance on resource-intensive laboratory experiments, reducing costs and environmental impact.

**TABLE 1**
**SMALL MOLECULE DATABASES AND COMPOUND COLLECTIONS AVAILABLE FROM VENDORS OR INSTITUTIONS**

| Database | Type | No. | Website |
|---|---|---|---|
| ZINC [100] | Public | 13 million | http://zinc.docking.org |
| ChemDB [101] | Public | 5 million | http://cdb.ics.uci.edu |
| eMolecules | Commercial | 7 million | http://www.emolecules.com |
| ChemSpider | Public | 26 million | http://www.chemspider.com |
| Pubchem | Public | 30 million | http://pubchem.ncbi.nlm.nih.gov |
| ChemBank [102] | Public | 1,2 million | http://chembank.broadinstitute.org |
| DrugBank [103, 104] | Public | 4,800 drugs; 2,500 targets | http://www.drugbank.ca |
| NCI Open Database | Public | 265,000 | http://cactus.nci.nih.gov/ncidb2.2/ |
| Chimiothèque Nationale | Commercial | 48,370 | http://chimiotheque-nationale.enscm.fr/?lang=fr |
| Drug Discovery Center Collection | Commercial | 340,000 | http://www.drugdiscovery.uc.edu/ |
| ChEMBL [105] | Public | 1 million | http://www.ebi.ac.uk/chembldb/index.php |
| WOMBAT [106] | Commercial | 263,000 | http://www.sunsetmolecular.com |
| ChemBridge | Commercial | 700,000 | http://www.chembridge.com |
| Specs | Commercial | 240,000 | http://www.specs.net |
| CoCoCo [107] | Public | 7 million | http://cococo.unimore.it/tiki-index.php |
| Asinex | Commercial | 550,000 | http://www.asinex.com |
| Enamine | Commercial | 1,7 million | http://www.enammine.net |
| Maybridge | Commercial | 56,000 | http://www.maybridge.com |
| ChemDiv | Commercial | 1,5 million | http://www.chemdiv.com |
| ACD | Commercial | 3,9 million | http://accelrys.com/products/databases/sourcing/avaible-chemicalsdirectory.html |
| MDDR | Commercial | 150,000 | http://accelerys.com/products/databases/bioactivity/mddr.html |

**TABLE 2**
**EXAMPLE OF COMMONLY USED DOCKING SOFTWARE**

| Software | Free for Academia | Website |
|---|---|---|
| AUTODOCK [109] | Yes | http://autodock.scripps.edu/ |
| DOCK [110] | Yes | http://dock.compbio.ucsf.edu/ |
| FlexX [111] | No | http://www.biosolveit.de/flexx/ |
| GLIDE [112] | No | http://www.schrodinger.com/ |
| GOLD [113] | No | http://www.ccdc.cam.ac.uk/products/life_sciences/gold/ |
| EADock [114] | No | http://lausanne.isb-sib.ch/~agrosdid/projects/eadock/eadock_dss.php |

**TABLE 3**
**TARGETED SMALL MOLECULES DATABASES FROM COMMERCIAL VENDORS**

| Company | Library Name | Link Address |
|---|---|---|
| Asinex | Antibacterials | http://www.asinex.com |
| SPECS | Kinase-targeted Library | http://www.specs.net/ |
| Timtec | GPCR Ligands | http://www.timtec.net |
| | Kinase Modulators | |
| | Protease Inhibitors | |
| | Potassium Channels Modulators | |
| | Nuclear Receptors Ligands | |
| ChemBridge | Kinase-Biased Sets | http://www.chembridge.com |
| | GPCR Library | |
| | Channel-Biased Sets | |
| ChemDiv | GPCRs | http://www.chemdiv.com/main.phtml |
| | Kinases | |
| InterBioScreen | IBS High-Hit Databases | http://www.ibscreen.com |
| | Analgesics | |
| | Antibacterials | |
| | Antidiabetics | |
| | Cancerostatics | |
| | Cns regulators | |
| MayBridge | | http://www.maybridge.com |
| Key Organics | Bionet | http://www.keyorganics.ltd.uk |
| | Antimalarial Agents | |
| | Active Compounds for Cancer Research | |
| | Active Compounds for CNS Research | |
| Life Chemicals | GPCR Library | http://lifechemicals.emolecules.com/ |
| | Kinase Library | |
| | Anticancer Library | |

**TABLE 4**
**EXAMPLE OF COMMONLY USED DOCKING SOFTWARE**

| Software | Free for Academia | Website |
|---|---|---|
| Surflex [115] | No | http://www.tripos.com/index.php |
| ICM [116] | No | http://www.molsoft.com/docking.html |
| LigandFit [117] | No | http://accelrys.com/products/discovery-studio |
| eHiTS [118] | No | http://www.simbiosys.ca/ehits/index.html |
| SLIDE [119] | Yes on demand | http://www.bch.msu.edu/~kuhn/software/slide/index.html |
| ROSETTA_DOCK [120] | Yes on demand | http://rosettadock.graylab.jhu.edu/ |
| Virtual Docker [111] | No | http://www.molegro.com/mvd-product.php |
| Ligand-Receptor Docking [112] | No | http://www.chemcomp.com/software-sbd.htm |
| FRED [113] | Yes on demand | http://www.eyesopen.com/oedocking |
| ZDOCK [114] | Yes | http://zlab.umassmed.edu/zdock/ |

**TABLE 5**
**DOCKING PROGRAMS THAT INCLUDE PROTEIN FLEXIBILITY**

| Program and Ref. | Ligand Flexibility | Protein Flexibility | Scoring function |
|---|---|---|---|
| AUTODOCK4 [109] | Evolutionary algorithm | Flexible side chain | Force field |
| DOCK [110] | Incremental build | Protein side chain and flexibility | Force field or contact score |
| GOLD [113] | Evolutionary algorithm | Protein side chain and backbone flexibility | Empirical score |
| EADock [114] | Evolutionary algorithm | Flexible side chain and backbone | Force field |
| ICM, IFREDA [116] | Pseudo-Brownian sampling and local minimization | Flexible side chains | Force field and Empirical score |
| FlexE [124] | Incremental build | Ensemble of protein structure | Empirical score |
| GLIDE Induced Fit [125] | Exhaustive search | Flexible side chains | Empirical score |

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**REFERENCES**

[1] Gunther, F. A., & Jeppson, L. R. (1960). Modern insecticides and world food production.

[2] Sharma, S., Kooner, R., & Arora, R. (2017). Insect pests and crop losses. *Breeding insect resistant crops for sustainable agriculture*, 45-66.

[3] Godfray, H.C.J., Beddington, J.R., Crute, I.R., Haddad, L., & Lawrence, D. (2010) Food security: the challenge of feeding 9 billion people. *Science*, 327, 812-818.

[4] Damalas, C. A., & Eleftherohorinos, I. G. (2011). Pesticide exposure, safety issues, and risk assessment indicators. *International journal of environmental research and public health*, *8*(5), 1402-1419.

[5] Hashemi, S. M., & Damalas, C. A. (2010). Farmers' perceptions of pesticide efficacy: reflections on the importance of pest management practices adoption. *Journal of Sustainable Agriculture*, *35*(1), 69-85.

[6] Oerke EC and Dehne HW, Safeguarding production-losses in major crops and the role of crop protection. *Crop Protection*, 23:275–285 (2004).

[7] Saravi SSS and Shokrzadeh M, Role of pesticides in human life in the modern age: a review. Pesticides in the Modern World-Risks and Benefits 5:3–12 (2011).

[8] Lorsbach BA and Sparks TC, Innovations in agrochemical discovery and the role of metabolism, bioavailability and formulations. Pest Manag Sci 73:655–657 (2017). 4

[9] Xiao Y, Chang T, Song Q, Wang S, Tholen D, Wang Y, Xin CP, Zheng GY, Zhao HL and Zhu XG, ePlant for quantitative and predictive plant science research in the big data era—Lay the foundation for the future model guided crop breeding, engineering and agronomy. Quant Biol 5:260–271 (2017).

[10] Sun C, Li F, Wei M, Xiang ZX, Chen CJ and Xu dl, Detection and biological characteristics of Alternaria alternata resistant to difenoconazole from Paris polyphylla var. chinensis, an indigenous medicinal herb. Plant Dis 105:1546–1554 (2021).

[11] Panikar S, Shoba G, Arun M, Sahayarayan JJ, Usha Raja Nanthini A and Chinnathambi A, Essential oils as an effective alternative for the treatment of COVID-19: molecular interaction analysis of protease (Mpro) with pharmacokinetics and toxicological properties. J Infect Public Health 14:601–610 (2021).

[12] Zhao W, Huang Y and Hao GF, Pesticide informatics expands the opportunity for structure-based molecular design and optimization. Adv Agrochem 1:147 (2022).

[13] Quds R, Hashmi MA and Iqbal Z, Interaction of mancozeb with human hemoglobin: spectroscopic, molecular docking and molecular dynamic simulation studies. Spectrochim Acta A 280:121503 (2022).

[14] Shoichet BK, McGovern SL, Wei B and Irwin JJ, Lead discovery using molecular docking. Curr Opin Chem Biol 6:439–446 (2002).

[15] Goosey MW, Towards the rational design of crop protection agents. Pestic Sci 34:313–320 (1992).

[16] Sparks TC and Duke SO, Structure simplification of natural products as a lead generation approach in agrochemical discovery. J Agric Food Chem 69:8324–8346 (2021).

[17] Sparks TC and Bryant RJ, Impact of natural products on discovery of, and innovation in, crop protection compounds. Pest Manag Sci 78: 399–408 (2022).

[18] Hao GF, Wang F, Li H, Zhu XL, Yang WC, Huang LS, Wu JW, Edward Ab and Yang GF, Computational discovery of Picomolar Q o site inhibitors of cytochrome bc1 complex. J Am Chem Soc 134:11168–11176 (2012).

[19] Loch AR, Lippa KA, Carlson DL, Chin YP, Traina SJ and Roberts AL, Nucleophilic aliphatic substitution reactions of propachlor, alachlor, and metolachlor with bisulfide (HS−) and Polysulfides (Sn 2−). Environ Sci Technol 36:4065–4073 (2002).

[20] Masayuki N and Crosby DG, Photonucleophilic reactions of nitrofen. J Agric Food Chem 22:930–933 (1974).

[21] Asami T, Mizutani M and Shimada Y, Triadimefon, a fungicidal triazole-type P450 inhibitor, induces brassinosteroid deficiency-like phenotypes in plants and binds to DWF4 protein in the brassinosteroid biosynthesis pathway. Biochem J 369:71–76 (2003).

[22] Sparks TC and Lorsbach BA, Perspectives on the agrochemical industry and agrochemical discovery: perspectives on the agrochemical industry and agrochemical discovery. Pest Manag Sci 73:672–677 (2017).

[23] Boudebbouz A, Boudalia S, Boussadia MI, Gueroui Y, Habila S and Bousbia A, Pesticide residues levels in raw cow's milk and health risk assessment across the globe: a systematic review. Environ Adv 10: 100266 (2022).

[24] El-Nahhal I, Pesticide residues in drinking water, their potential risk to human health and removal options.J Environ Manage 299:113611 (2021).

[25] Sharma KK, Tripathy V, Sharma K, Gupta R, Yadav R and Devi S, Long– term monitoring of 155 multi–class pesticide residues in Indian vegetables and their risk assessment for consumer safety. Food Chem 373:131518 (2022).

[26] Li Z, Modeling pesticide residues in nectar and pollen in support of pesticide exposure assessment for honeybees: a generic modeling approach. Ecotoxicol Environ Saf 236:113507 (2022).

[27] Ding F, Li LX, Peng W, Peng YK and Liu BQ, Molecular basis for the resistance of American sloughgrass to aryloxyphenoxypropionic acid pesticides and its environmental relevance: a combined experimental and computational study. Chemosphere 235:1030–1040 (2019).

[28] Ahmed S, Siddique MA, Rahman M, Bari ML and Ferdousi S, A study on the prevalence of heavy metals, pesticides, and microbial contaminants and antibiotics resistance pathogens in raw salad vegetables sold in Dhaka, Bangladesh. Heliyon 5:e01205 (2019).

[29] Brausch JM and Smith PN, Pesticide resistance from historical agricultural chemical exposure in Thamnocephalus platyurus (Crustacea: Anostraca). Environ Pollut 157:481–487 (2009).

[30] Liu P, Zhang L, Li H, Wei Y, Wu F and You J, Reduced concentrations and toxicity of sediment-associated pesticides from vegetable planting field to surrounding waterways: impacts of chemical properties and intrinsic toxicity. J Hazard 436:129292 (2022).

[31] Ahmed MAI, Ahmed AMM, Malafaia G and Elghareeb TA, Octopamine receptor agonists synergistically increase the selected pesticides' toxicity in Rhopalosiphum padi: perspectives for reducing pesticide use, emergence of resistant strains and environmental impacts. J Hazard 6:100069 (2022).

[32] Tai H, Zhang F, Xiao C, Tang R, Liu Z, Bai S and Wang ZY, Toxicity of chemical pesticides commonly used in maize to *Trichogramma ostriniae* (Hymenoptera: Trichogrammatidae), an egg parasitoid of Asian corn borer. *Ecotoxicol Environ Saf*, 241,113802 (2022).

[33] Veedu SK, Ayyasamy G, Tamilselvan H and Ramesh M, Single and joint toxicity assessment of acetamiprid and thiamethoxam neonicotinoids pesticides on biochemical indices and antioxidant enzyme activities of a freshwater fish Catla catla. Comp Biochem Physiol C Toxicol Pharmacol 257:109336 (2022).

[34] Xu D, He Y, Zhang Y, Xie W, Wu Q and Wang S, Status of pesticide resistance and associated mutations in the two-spotted spider mite, Tetranychus urticae, in China. Pestic Biochem Physiol 150: 89-96 (2018).

[35] Vaidya AS, Helander JDM, Peterson FC, Elzinga D, Dejonghe W and Kaundal A, Dynamic control of plant water use using designed ABA receptor agonists. Science 366: eaaw8848 (2019).

[36] Kharkar PS, Warrier S and Gaud RS, Reverse docking: a powerful tool for drug repositioning and drug rescue. Future Med Chem 6:333– 342 (2014).

[37] Lee A, Lee K and Kim D, Using reverse docking for target identification and its applications for drug discovery. Expert Opin Drug Dis 11:707– 715 (2016).

[38] Chen F, Wang Z, Wang C, Xu Q, Liang J, Xu X, Yang JB, Wang CY, Jiang T and Yu RL, Application of reverse docking for target prediction of marine compounds with anti-tumor activity. J Mol Graph Model 77:372–377 (2017).

[39] Zhou Y, Chen L and Hu J, Resistance mechanisms and molecular docking studies of four novel QoI fungicides in Peronophythora litchii. Sci Rep 5:1–10 (2015).

[40] Sharma D and Bisht DM, Tuberculosis hypothetical proteins and proteins of unknown function: hope for exploring novel resistance mechanisms as well as future target of drug resistance. Front Microbiol 8:465 (2017).

[41] Mamidala P, Wijeratne AJ and Wijeratne S, RNA-Seq and molecular docking reveal multi-level pesticide resistance in the bed bug. BMC Genomics 13:1–17 (2012).

[42] Li H, Sze KH and Lu G, Machine-learning scoring functions for structure-based drug lead optimization. Wires Comput Mol Sci 10: e1465 (2020).

[43] Crampon K, Giorkallos A, Deldossi M, Baud S and Steffenel LA, Machine-learning methods for ligand–protein molecular docking. Drug Discov Today 27:151–164 (2022).

[44] Jiang D, Hsieh CY, Wu Z, Kang Y, Wang J, Wang E, BEN l, Shen C, XU l, Wu J, Cao DS and Hou TJ, Interactiongraphnet: a novel and efficient deep graph representation learning framework for accurate protein–ligand interaction predictions. J Med Chem 64:18209–18232 (2021).

[45] Xia F, Sun K, Yu S, Aziz A, Wan L, Pan S and Liu H, Graph learning: a survey. IEEE Trans Artif Intell 2:109–127 (2021).

[46] Gentile F, Agrawal V, Hsing M, Ton AT, Ban F, Norinder U et al., Deep docking: a deep learning platform for augmentation of structure based drug discovery. ACS Central Sci 6:939–949 (2020).

[47] Tang M, Wen C and Lin J, Discovery of novel A2AR antagonists through deep learning-based virtual screening. Artificial Intelligence in the Life Sciences 3:100058 (2023).

[48] Fu, Y., Sun, Y. N., Yi, K. H., Li, M. Q., Cao, H. F., Li, J. Z., & Ye, F. (2018). Combination of virtual screening protocol by in silico toward the discovery of novel 4-hydroxyphenylpyruvate dioxygenase inhibitors. *Frontiers in Chemistry*, 6, 14.

[49] Chen YC, Beware of docking! Trends Pharmacol Sci 36:78–95 (2015).

[50] Warren GL, Andrews CW, Capelli A-M, Clarke B, LaLonde J and Lambert MH, Assessment of docking programs and scoring functions. J Med Chem 49:5912–5931 (2006).

[51] Mohan V, Gibbs A, Cummings M, Jaeger E and DesJarlais R, Docking: successes and challenges. CPD 11:323–333 (2005).

[52] Warren GL, Do TD, Kelley BP, Nicholls A and Warren SD, Essential considerations for using protein–ligand structures in drug discovery. *Drug Discov Today* 17:1270–1281 (2012).

[53] Ferreira L, dos Santos R, Oliva G and Andricopulo A, Molecular docking and structure-based drug design strategies. Molecules 20: 13384–13421 (2015).

[54] Agarwal S and Mehrotra R, An overview of molecular docking. JSM Chem 4:1024–1028 (2016).

[55] Gschwend DA, Good AC and Kuntz ID, Molecular docking towards drug discovery. J Mol Recognit 9:175–186 (1996).

[56] Huang SY and Zou X, Advances and challenges in protein-ligand docking. IJMS 11:3016–3034 (2010).

[57] García-Godoy MJ, López-Camacho E, García-Nieto J, Del Ser J, Nebro AJ and Aldana-Montes JF, Bio-inspired optimization for the molecular docking problem: state of the art, recent results and perspectives. Appl Soft Comput 79:30-45 (2019).

[58] Fischer E, Influence of configuration on the action of enzymes. Ber. Dtsch. Chem. Ges 27:2985–2993 (1894).

[59] Meiler J and Baker D, ROSETTALIGAND: protein-small molecule docking with full side-chain flexibility. Proteins 65:538–548 (2006).

[60] Kim KH, Outliers in SAR and QSAR: 2. Is a flexible binding site a possible source of outliers? J Comput Aided Mol Des 21:421–435 (2007).

[61] Mobley DL and Dill KA, Binding of small-molecule ligands to proteins: "what you see" is not always "what you get". Structure 17:489–498 (2009).

[62] Gutteridge A and Thornton J, Conformational changes observed in enzyme crystal structures upon substrate binding. J Mol Biol 346: 21–28 (2005).

[63] Cong X, Zhang X, Liang X, He X, Tang Y, Zheng X, Lu SY, Zhang JY and Chen T, Delineating the conformational landscape and intrinsic properties of the angiotensin II type 2 receptor using a computational study. Comput Struct Biotec 20:2268–2279 (2022).

[64] Koshland DE, Application of a theory of enzyme specificity to protein synthesis. Proc Natl Acad Sci USA 44:98-104 (1958).

[65] Tu, M., Cheng, S., Lu, W., & Du, M. (2018). Advancement and prospects of bioinformatics analysis for studying bioactive peptides from food-derived protein: Sequence, structure, and functions. *Trends in Analytical Chemistry*, 105, 7-17.

[66] Huang, S. Y., & Zou, X. (2008). Advances and challenges in protein-ligand docking. *International Journal of Molecular Sciences*, 9(10), 1721-1740.

[67] Forli, S., Huey, R., Pique, M. E., Sanner, M. F., Goodsell, D. S., & Olson, A. J. (2016). Computational protein-ligand docking and virtual drug screening with the AutoDock suite. *Nature Protocols, 11*(5), 905-919.

[68] Morris GM, Huey R, Lindstrom W (2009) AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. J Comput Chem 30:2785–2791.

[69] Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., & Bourne, P. E. (2000). The Protein Data Bank. *Nucleic Acids Research, 28*(1), 235-242.

[70] Pettersen EF, Goddard TD, Huang CC et al (2004) UCSF Chimera-a visualization system for exploratory research and analysis. J Comput Chem 25:1605–1612.

[71] Laskowski, R. A., MacArthur, M. W., Moss, D. S., & Thornton, J. M. (1993). PROCHECK: a program to check the stereochemical quality of protein structures. *Journal of Applied Crystallography*, *26*(2), 283-291.

[72] Kim, S., Thiessen, P. A., Bolton, E. E., Chen, J., Fu, G., Gindulyte, A., & Bryant, S. H. (2016). PubChem substance and compound databases. *Nucleic acids research*, 44(D1), D1202-D1213.

[73] Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 31(2), 455-461.

[74] Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews*, 64, 4-17.

[75] Tetko, I. V., & Bruneau, P. (2004). Application of ALOGPS 2.1 to predict log D distribution coefficient for Pfizer proprietary compounds. Journal of Medicinal Chemistry, 47(23), 5601-5604.

[76] Ertl, P., Rohde, B., & Selzer, P. (2000). Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. Journal of Medicinal Chemistry, 43(20), 3714-3717.

[77] Ghose, A. K., Viswanadhan, V. N., & Wendoloski, J. J. (1998). A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. Journal of Combinatorial Chemistry, 1(1), 55-68.

[78] Manallack, D. T. (2007). The pKa distribution of drugs: application to drug discovery. Perspectives in Medicinal Chemistry, 1, 25-38.

[79] Delaney, J. S. (2004). ESOL: estimating aqueous solubility directly from molecular structure. Journal of Chemical Information and Computer Sciences, 44(3), 1000-1005.

[80] Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004; 3(11):935–949.

[81] Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. Current computer-aided drug design, 7(2), 146-157.

[82] Karplus, M., & McCammon, J. A. (2002). Molecular dynamics simulations of biomolecules. Nature Structural Biology, 9(9), 646-652.

[83] Lindahl, E., Hess, B., & van der Spoel, D. (2001). GROMACS 3.0: A package for molecular simulation and trajectory analysis. Journal of Molecular Modeling, 7(8), 306-317.

[84] Hollingsworth, S. A., & Dror, R. O. (2018). Molecular dynamics simulation for all. Neuron, 99(6), 1129-1143.

[85] Plattner, N., & Noé, F. (2015). Protein conformational plasticity and complex ligand-binding kinetics explored by atomistic simulations and Markov models. Nature Communications, 6, 7653.

[86] Abraham, M. J., Murtola, T., Schulz, R., Páll, S., Smith, J. C., Hess, B., & Lindahl, E. (2015). GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX, 1-2, 19-25.

[87] Case, D. A., Cheatham, T. E., Darden, T., Gohlke, H., Luo, R., Merz, K. M., ... & Kollman, P. A. (2005). The Amber biomolecular simulation programs. Journal of Computational Chemistry, 26(16), 1668-1688.

[88] Brooks, B. R., Brooks, C. L., Mackerell, A. D., Nilsson, L., Petrella, R. J., Roux, B., ... & Karplus, M. (2009). CHARMM: The biomolecular simulation program. Journal of Computational Chemistry, 30(10), 1545-1614.

[89] Humphrey, W., Dalke, A., & Schulten, K. (1996). VMD: Visual molecular dynamics. Journal of Molecular Graphics, 14(1), 33-38.

[90] Lindorff-Larsen, K., Piana, S., Palmo, K., Maragakis, P., Klepeis, J. L., Dror, R. O., & Shaw, D. E. (2010). Improved side-chain torsion potentials for the Amber ff99SB protein force field. Proteins: Structure, Function, and Bioinformatics, 78(8), 1950-1958.

[91] Maden, S. F., Sezer, S., & Acuner, S. E. (2022). Fundamentals of Molecular Docking and Comparative Analysis of Protein–Small-Molecule Docking Approaches. In Molecular Docking-Recent Advances. IntechOpen.

[92] Huang, N., Shoichet, B. K., & Irwin, J. J. (2006). *Journal Medicinal Chemistry*, 49(23), 789-801.

[93] Raval, K., & Ganatra, T. (2022). *IP International Journal Comprehensive Advance Pharmacology*, 7(1), 12-16.

[94] Ahmad, A., Javed, M. R., Rao, A. Q., Khan, M. A., Ahad, A., Shahid, A. A., & Husnain, T. (2015). *Frontiers in Plant Science*, 6, 152923.

[95] Benslama, O., Mansouri, N., & Arhab, R. (2021). *Earth and Environmental Science*, 910 (1), 12023.

[96] Gurbuz-Colak, N. (2023). *The Eurasia Proceedings of Science, Technology, Engineering and Mathematics*, 25, 26-34.

[97] Rodrigues, G. C. S., dos Santos Maia, M., Silva Cavalcanti, A. B., de Sousa, N. F., Scotti, M. T., & Scotti, L. (2021). In silico studies of lamiaceae diterpenes with bioinsecticide potential against Aphis gossypii and Drosophila melanogaster. *Molecules*, *26*(3), 766.

[98] Khanna, S., Sharma, S., Kumari, M., Tyagi, K., Handique, J., Mishra, L., ... & Mayandi, D. G. (2023). Molecular docking of triterpenoids from Neem with the ecdysone receptor of lepidopteran pests.

[99] Nakao, T., Banba, S., Nomura, M., & Hirase, K. (2013). Meta-diamide insecticides acting on distinct sites of RDL GABA receptor from those for conventional noncompetitive antagonists. *Insect biochemistry and molecular biology*, *43*(4), 366-375.

[100] Irwin, J.J.; Shoichet, B.K. ZINC: a free database of commercially available compounds for virtual screening. *J. Chem. Inf. Model*., 2005, *45*(1), 177-182.

[101] Chen, J.H.; Linstead, E.; Swamidass, S.J.; Wang, D.; Baldi, P. ChemDB update: full-text search and virtual chemical space. *Bioinformatics*, 2007, *23*(17), 2348-2351.

[102] Seiler, K.P.; George, G.A.; Happ, M.P.; Bodycombe, N.E.; Carrinski, H.A.; Norton, S.; Brudz, S.; Sullivan, J.P.; Muhlich, J.; Serrano, M.; Ferraiolo, P.; Tolliday, N.J.; Schreiber, S.L.; Clemons, P.A. ChemBank: a small-molecule screening and cheminformatics resource database. *Nucleic Acids Res*., 2008, *36*(database issue), D351-D359.

[103] Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.*, 2006, *34*(database issue), D668-D672.

[104] Knox, C.; Law, V.; Jewison, T.; Liu, P.; Ly, S.; Frolkis, A.; Pon, A.; Banco, K.; Mak, C.; Neveu, V.; Djoumbou, Y.; Eisner, R.; Guo, A. C.; Wishart, D. S. DrugBank 3.0: a comprehensive resource for "omics" research on drugs. *Nucleic Acids Res.*, 2011, *39*(database issue), D1035-D1041.

[105] Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; AlLazikani, B.; Overington, J. P. ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res.*, 2012, *40*(D1), D1100-D1107.

[106] Olah, M.; Mracec, M.; Ostopovici, L.; Rad, R.; Bora, A.; Hadaruga, N.; Olah, I.; Banda, M.; Simon, Z.; Mracec, M.; and Oprea, T.I. In: *Chemoinformatics in Drug Discovery*; Oprea, Ed.; WileyVCH Verlag GmbH.: Weinheim, 2005; Vol. *23*, pp. 221-239.

[107] Del Rio, A.; Barbosa, A. J. M.; Caporuscio, F.; Mangiatordi, G. F. CoCoCo: a free suite of multiconformational chemical databases for high-throughput virtual screening purposes. *Mol. BioSyst.*, 2010, *6*(11), 2122-2128.

[108] Morris, G. M.; Goodsell, D. S.; Halliday, R.S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *J. Comput. Chem.*, 1998, *19*(14), 1639-1662.

[109] Ewing, T. J.; Makino, S.; Skillman, A. G.; Kuntz, I. D. DOCK 4.0: search strategies for automated molecular docking of flexible molecule databases. *J. Comput. Aided Mol. Des.* 2001, *15*(5), 411428.

[110] Warren, G. L. *et al.* A critical assessment of docking programs and scoring functions. *J. Med. Chem.*, 2006, *49*(20), 5912-5931.

[111] Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Francis, P.; Shenkin, P. S. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.*, 2004, *47*(7), 17391749.

[112] Verdonk, M. L.; Cole, J. C.; Hartshorn, M. J.; Murray C. W.; Taylor, R. D. Improved protein-ligand docking using GOLD *Proteins*, 2003, *52*(4), 609-623.

[113] Grosdidier, A.; Zoete, V.; Michielin, O. EADock: Docking of small molecules into protein active sites with a multiobjective evolutionary optimization. *Proteins*, 2007, *67*(4), 1010-1025.

[114] Jain, A. N. Surflex-Dock 2.1: Robust performance from ligand energetic modeling, ring flexibility, and knowledge-based search. *J. Comput. Aided Mol. Des.* 2007, *21*(5), 281-306.

[115] Abagyan, R.; Totrov, M.; Kuznetsov, D. N. ICM: a new method for protein modeling and design. Applications to docking and structure prediction from the distorted native comformation. *J. Comput. Chem.*, 1994, *15*(5), 488506.

[116] Böhm, H. J. The development of a simple empirical scoring function to estimate the binding constant for a protein-ligand complex of known three-dimensional structure. *J. Comput. Aided Mol. Design*, 1994, *8*(3), 243-256.

[117] Ravitz, O.; Zsoldos, Z.; Simon, A. Improving molecular docking through eHiTS' tunable scoring function. *J. Comput. Aided Mol. Des.*, 2011, *25*(11), 1033-1051.

[118] Zavodszky, M. I.; Rohatgi, A.; Van Voorst, J. R.; Yan, H.; Kuhn, L. A. Scoring ligand similarity in structure-based virtual screening. *J. Mol. Recognit.*, 2009, *22*(4), 280-292.

[119] Gray, J. J.; Moughan, S. E.; Wang, C.; Schueler-Furman, O.; Kuhlman, B.; Rohl, C. A.; Baker, D. Protein-protein docking with simultaneous optimization of rigid-body displacement and sidechain conformations. *J. Mol. Biol.*, 2003, *331*(1), 281-299.

[120] Thomsen, R.; Christensen, M. H. MolDock: A new technique for high-accuracy molecular docking. *J. Med. Chem.*, 2006, *49*(11), 3315-3321.

[121] *Molecular Operating Environment (MOE)*, 2012.10; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2012.

[122] McGann, M. FRED and HYBRID docking performance on standardized datasets. *J. Comput. Aided Mol. Des.*, 2012, *26*(8), 897906.

[123] Chen, R.; Li, L.; Weng, Z. ZDOCK: An initial-stage proteindocking algorithm. *Proteins*, 2003, *52*(1), 80-87.

[124] Perez, A.; Yang, Z.; Bahar, I.; Dill, K. A.; MacCallum, J. L. FlexE: using elastic network models to compare models of protein structure. *J. Chem. Theory Comput.*, 2012, *8*(10), 3985-399.

[125] Sherman, W.; Day, T.; Jacobson, M. P.; Friesner, R. A.; Farid, R. Novel procedure for modeling ligand/receptor induced fit effects. *J. Med. Chem.*, 2006, *49*(2), 534-553.