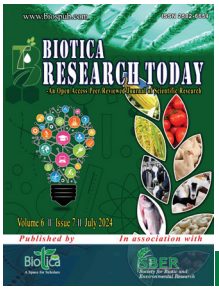
Bio. Res. Today 2024, 6(7):397-400



Biotica Research Today

e-ISSN: 2582-6654

July, 2024

Article ID: RT1708 **Popular Article**

Computer Aided Drug Design (CADD): A New Frontier in Plant Disease Control

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Conflict of interests: The author has declared that no conflict of interest exists.

How to cite this article?

Chetan, K.K., Divyashree, Ashwini, J.H., *et al*., 2024. Computer Aided Drug Design (CADD): A New Frontier in Plant Disease Control. *Biotica Research Today* 6(7), 397-400.

Abstract

Plant diseases pose a significant threat to global food security. While traditional methods like pesticides and resistant crop varieties have been employed, the development of novel control strategies remains crucial. Recent advancements in understanding the molecular mechanisms of plant pathogens have opened new avenues for targeted interventions. Computer-aided drug design (CADD), a technique successfully applied in pharmaceutical research, holds immense potential for the discovery of effective agrochemicals. CADD is a specialized field that employs computational techniques to simulate how drugs interact with their target molecules. This approach relies on principles from quantum mechanics and molecular modeling to explore methods like structure-based drug design, ligand-based drug design and database searching. By predicting binding affinity, CADD has been instrumental in identifying potent compounds against plant pathogens. The rapid growth of genomic and structural data, coupled with sophisticated computational tools, creates unprecedented opportunities to leverage CADD for addressing plant disease challenges.

Keywords: Agrochemical, CADD, Disease management, Molecular modeling

Introduction

Traditionally, the development of chemicals was based on study on indigenous traditional knowledge, or it was a fortuitous discovery made by identifying the active ingredient from traditional cures (Shanmugam and Jeon, 2017). The uncertainty associated with finding a chemical molecule that functions as a medicine led to the discovery of penicillin, which turned drug discovery into an exciting field of study. In the conventional discovery method, computer software is not required for the screening and optimisation of chemical compounds. The screening process is the most time-consuming part of this approach since it requires screening millions of compounds, which takes time and there is no guarantee that we will obtain the chemical. This procedure will need more than 12 years and up to 800 billion rupees in development costs. Agrochemical scientists are searching for more opportunistic methods, such computer-aided drug design (CADD), which is time and money-efficient, to get over these limitations (Ugariogu *et al.*, 2020).

The process of finding agrochemicals via the use of computational resources and technologies is known as CADD (Shanmugam and Jeon, 2017). Biological databases and tools are necessary for a successful drug discovery process. This method is essentially used to investigate structural biology in order to understand how proteins regulate biological processes, the interaction between drug and receptor molecular structures and functions and how their shapes and charges complement one other. With the use of statistical techniques and specialised biology software, drug discovery in the modern era expedites the screening and refining of agrochemical compounds (Ugariogu *et al.*, 2020).

CADD in Plant Pathology

The technique uses a multidisciplinary approach from several fields, including information technology, bioinformatics, biochemistry, toxicology and biophysical chemistry. The method primarily makes use of biological databases and biological process design tools. Plant pathology, in particular diseases of plants caused by bacteria, viruses and

Article History

RECEIVED on 22nd July 2024 RECEIVED in revised form 29th July 2024 ACCEPTED in final form 30th July 2024

fungus, generates toxins, polysaccharides, enzymes and pathogenic proteins that aid in the spread of disease. Using this method, it is easier to target these macromolecules for the creation of an antibiotic or pesticide (Shanmugam and Jeon, 2017). The main objective of CADD is to use information on molecular mechanics and dynamics to predict which molecules, out of many, will attach to a target and, if so, how strongly. The basic work flow includes target identification, target validation, lead ligand discovery, lead optimization, laboratory trials and field trials (Figure 1). The primary goals of using the CADD approach in plant pathology are as follows: 1) To improve the screening of fungicide molecules using computer-aided software, which will speed up the fungicide discovery process; 2) To prevent fungicide resistance issues by deeply understanding the molecular mechanism of action of fungicide on fungi; 3) To comprehend the molecular events of disease management; and 4) Lastly, to develop more effective agrochemicals that are more target specific, effective and efficient in action.

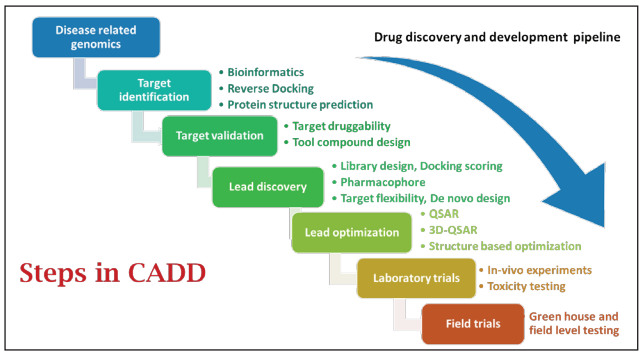

Figure 1: Basic steps in drug discovery and development

Types of Computer-Aided Drug Discovery (CADD)

The CADD approach is broadly classified into two types based on the molecules discovered and the purpose, *viz.,* 1) Ligand-based drug discovery, 2) Structure-based drug discovery.

Ligand-based Drug Discovery (LBDD)

The method involves the discovery of drug molecules based on existing data of drug molecules. Drug molecules and their information are well-known in this method, but the target is unknown. Drug molecules are discovered on the basis of drug physicochemical properties. This method is less established and has little importance in agrochemical discovery because plant pathogens secrete macromolecules to develop diseases in plants. These macromolecules act as biological targets for the development of ligands. Ligands with drug properties may not always be targeted to these pathogenic proteins and it is uncertain that they can be used on pathogenic targets. The chances of success screening drug molecules that specifically act on plant pathogenic substances are rare. Therefore, this approach is not popular in the agrochemical drug discovery process.

Structure-based Drug Discovery (SBDD)

The method involves information on the biological target and its active site. Here the drug molecules are filtered to find the suitable compound that can attach to the active site properly and, in turn, modifies the biological target. Here the 3-D structure is useful for identifying binding sites present in the target and the exploration of ligand binding pockets. The 3-D structure depicts information on hetero atoms, no. of H bond donor, H bond acceptor, anionic and cationic properties and amino acid residues in the active site. Candidate drugs with more selectivity and affinity to the target are designed based on the physicochemical properties of the active site of the target. The drug discovered can be used as an agrochemical by improving the drug features. This method is most promising in the agrochemical drug discovery process as it is target-directed drug discovery.

Homology Modelling

Also referred to as comparative protein modeling, involves creating a detailed 3D representation of a target protein using the known structure of a similar protein called a template. This method relies on the similarity of the target protein's amino acid sequence to that of the template. Typically, a sequence identity of at least 30% is necessary for generating a useful model. The accuracy of the constructed model is significantly influenced by the template's closeness to the target protein. Models based on templates with over 70% sequence identity are generally considered reliable enough for agrochemical research.

Pharmacophore Modelling

A pharmacophore model identifies essential molecular features necessary for a compound to interact with a specific biological target and trigger (or inhibit) a biological response. These features, such as hydrophobic regions, aromatic rings and hydrogen bond acceptors/donors, can be located on the ligand or projected onto the receptor. Pharmacophore models can be derived from active molecules (ligand-based) or by analyzing protein-ligand interactions (structure-based).

Molecular Docking

Molecular docking predicts the optimal orientation of a molecule (ligand) when bound to a target protein. It assesses the stability of the interaction, which is crucial for determining biological effects. By identifying potential binding sites on the protein, docking helps explore protein-ligand interactions.

Structure-Based Virtual Screening (SBVS)

SBVS is a computational method to discover new drug candidates. It compares 3D structures of compound libraries to the target protein's active site, identifying potential hits. These compounds are ranked based on predicted binding interactions, with top-ranked molecules selected for further evaluation.

Ligand-based Virtual Screening (LBVS)

LBVS uses a pharmacophore model to filter large compound libraries and identify potential ligands. It efficiently reduces the number of compounds for experimental testing by focusing on those with desired chemical features.

Agrochemical Validation

The compound identified is subjected to field trials and also ADME (Absorption, Distribution, Metabolism and Excretion) toxicity studies (if discovered agrochemicals are

used on fresh vegetables, a study is conducted to check residual nature in humans and animals). Further, it should not be phytotoxic or residual in plant cellular system. The dose should be optimized through a dose-response relationship. Formulations are specified and subjected to certification by respected authorities. QSAR (Quantitative structure-activity relationship) is also done for the predictors consisting of physicochemical properties or theoretical molecular descriptors of agrochemicals. Biological activity can be expressed quantitatively as the concentration of a substance required to give a certain biological response. The biological activity of molecules is usually measured in assays to establish the level of inhibition of particular metabolic pathways.

Computational Tools Used in the CADD Process

There are several computational tools needed in the drug discovery process using the SBDD approach. The technique needs software to obtain the target of interest and set of ligand molecules for the target by using freely accessible biological databases. The biological databases are NCBI, DDBJ, EMBL Protein Data Bank (PDB), Binding MOAD, PDB bind, MAYBRIDGE, DRUGBANK PubChem Database, chEMBL, Jchem, *etc*. To identify the ligand binding pockets as well as active sites in the biological target molecules. Software such as IntFOLD, RaptorX, Biskit, GeneSilico, MODELLER and MOE (Molecular Operating Environment) is preferred for this. For visualization and drawing the structure of target and ligand molecule in the cases where one finds a problem while designing, there is some software to handle the structural studies such as Rasmol, Raswin, Pymol for visualization and chem sketch, ACD CHEMSKETCH for drawing 3D structure to identify individual side chains in molecules. For molecular modeling & Homology modeling, in case no 3D structure is available for the protein of our interest, we need databases to find similar template sequences which have similar sequence identity with the target protein. Based on the template 3D structure, the drugs are designed. The development of homology models needs software such as Bioedit, ProModel, SWISS-MODEL, RaptorX, *etc*. For conducting molecular docking, there is software like AUTODOCK, PyRx, FleXx, *etc*. For ligand design screening and pharmacophore modeling, there is software such as LigandScout, PharmaGist, CHAAC, *etc*. (Ugariogu *et al.*, 2020).

CADD in Plant Disease Control: A Success Story

Researchers have made a significant stride in the battle against *Pseudomonas syringae*, a devastating plant pathogen. By employing cutting-edge computational techniques, they have identified a promising new drug candidate that could revolutionize disease control. The team (Shanmugam and Jeon, 2017) focused on two key enzymes essential for bacterial survival, MurD and MurE. Using advanced modeling techniques, they created precise 3D representations of these enzymes, despite the absence of experimental data. This groundbreaking achievement laid the foundation for the subsequent stages of the research.

Through a meticulous process of virtual screening and pharmacophore modeling, the researchers identified a compound with exceptional potential to inhibit the targeted enzymes. This compound, CD01278, demonstrated superior binding affinity to the modeled proteins, suggesting its effectiveness in disrupting the bacterial growth and survival (Shanmugam and Jeon, 2017). This discovery marks a pivotal moment in the development of new antimicrobial strategies. The identified compound holds immense promise as a lead molecule for creating novel and potent treatments to combat *Pseudomonas syringae* and potentially other bacterial infections. The successful application of computational methods in this research underscores the power of technology in accelerating drug discovery and development.

Another computational study by Krithika and Chellaram (2019) explored the potential of natural compounds from *Chitiniphilus shinanonensis* as antifungal agents. The study focused on four fungal pathogens: *Magnaporthe oryzae*, *Fusarium oxysporum*, *Colletotrichum* spp., and *Ustilago maydis*. Through molecular docking simulations, Asiatic acid and triterpene compounds isolated from *C. shinanonensis*, were evaluated for their binding affinity to target proteins from these pathogens. While both compounds showed interactions with all targets, the most promising results were observed against the Avr2 effector protein of *Fusarium oxysporum*. Analysis of the protein-ligand complexes revealed favourable binding interactions, including hydrogen and hydrophobic bonds, suggesting potential inhibitory effects of the compounds on the Avr2 protein. The calculated inhibition constant (Ki) for Asiatic acid and triterpene indicated their potential as lead compounds for further development as antifungal agents targeting *Fusarium oxysporum*. These findings provide a foundation for future experimental studies to validate the antifungal efficacy of Asiatic acid and triterpene against *Fusarium oxysporum* and other fungal pathogens.

Pros & Cons of CADD

Advantages

1. Efficiency: Homology modeling offers a significant reduction in both time and financial resources compared to traditional pesticide development, which can take over a decade and billions of rupees.

2. Precision: The target-oriented approach of homology modeling enhances accuracy in identifying potential pesticide targets.

3. Speed: Database screening accelerates the compound screening process, saving valuable time.

4. Insight: Provides detailed molecular information on diseases and the mechanisms by which fungicides interact with and inhibit target organisms.

Disadvantages

1. Data Limitations: Insufficient information about target and drug molecules, coupled with limited availability of suitable software and skilled personnel, can hinder the process.

2. Structural Information: The absence of 3D structures for many proteins has been a challenge, although the increasing number of plant pathogenic protein structures in databases

since 2016 is improving this situation (Baig *et al.*, 2016).

3. Complex Processes: Lead optimization and compound screening are time-consuming and require advanced technical expertise.

4. Simulation Challenges: Accurately simulating the complexities of biological systems remains a significant hurdle, even with cutting-edge techniques and computational power.

5. Uncertainty: Factors such as protein flexibility, conformational changes and the lack of experimental data on compound behaviour within cellular systems introduce uncertainties in the modeling process.

Conclusion

The adoption of techniques in pesticide industries will be a major breakthrough in achieving effective chemical discovery against plant diseases. The technique will empower researchers in molecular Plant Pathology with a deep understanding of the molecular aspects of disease management, fungicide resistance, active site variation, *etc*.

Future Aspects

The development of lead molecules against viral diseases needs to be addressed. In the development of viral diseases, the plant virus also secrets coat protein, movement protein and virulence factors, which can be easily targeted by the ligands. There is still less research on the identification of 3D structures for plant viral proteins because of this unavailability of structural information made this area unexplored.

References

Baig, M.H., Ahmad, K., Roy, S., Ashraf, J.M., Adil, M., Siddiqui, M.H., Khan, S., Kamal, M.A., Provazník, I., Choi, I., 2016. Computer aided drug design: Success and limitations. *Current Pharmaceutical Design* 22(5), 572-581. DOI: https://doi.org/10.2174/1381612822666151125000550.

Krithika, S., Chellaram C., 2019. Theoretical approach on targeting plant fungal pathogenic proteins against naturally isolated compounds from *Chitiniphilus shinanonensis*. *Asian Journal of Pharmaceutical and Clinical Research* 12(12), 138-142. DOI: https://doi.org/10.22159/ajpcr.2019.v12i12.35639.

Shanmugam, G., Jeon, J., 2017. Computer-aided drug discovery in plant pathology. *The Plant Pathology Journal* 33(6), 529-542. DOI: https://doi.org/10.5423/PPJ.RW.04.2017.0084.

Ugariogu, S.N., Duru, A., Abah, C.V., 2020. Natural product chemistry and computer aided drug design an approach to drug discovery: A review article. *International Journal of Pharmacognosy and Chinese Medicine* 4(3), 207-219. DOI: https://doi.org/10.23880/ipcm-16000207.