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Innovations in Computational Drug Design: The Impact of Structural Data and Molecular Docking

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ABSTRACT :

In recent years, Computer-Aided Drug Design (CADD) has become integral in both academic research and the pharmaceutical industry, demonstrating significant success in the discovery of potential drug candidates. Computer-Aided Drug Design (CADD) has achieved notable success in drug discovery, becoming a valuable tool in both academia and the pharmaceutical industry for identifying potential drug candidates. By leveraging structural information, CADD allows researchers to visualize and analyze the 3D structures of molecules using various docking programs. These programs evaluate the "docking score," which predicts how well a drug molecule, or ligand, binds to its target protein. Molecular docking, a core technique in CADD, supports virtual screening to optimize drug orientation, conformation, and positioning. Despite its complexity, including lead optimization and biological pathway analysis, molecular docking is advancing the field of drug design, aiding in both lead optimization and the development of new drug candidates.

Key Words: Computer-Aided Drug Design, Drug Discovery, Lead Optimization.

INTRODUCTION :

Drug Discovery and Development

Developing a new drug from a novel idea to expose of a finished product is a complex process which requires minimum of 12-15 years and cost more than $ 1 billion. The industry statistics suggest that, up to 10,000 compounds are synthesized and tested, up to 100 compounds are assessed for safety, but only 10 compounds are tested clinically in humans for every drug that is approved for medical use. Even when the new drug comes in the market its success is not assured shown in **(Fig: 1.1).**

In recent years, to overcome the difficulties medicinal chemistry has undergone revolutionary changes. Rapid developments in biological sciences helps in much better understanding of how human body functions at molecular level. To understand the structure and function of target, as well as mechanism of action by which it interacts with active drug is crucial to this approach.

- Drug discovery- Finding lead molecule

✓ Select a disease.
✓ Select a drug target.
✓ Identify a bioassay.
✓ Find a lead molecule.
✓ Isolation and purification of lead molecule if needed.
✓ Determine the structure of lead compound if require.

- Drug design

✓ Identification of structure-activity relationships (SARs).
✓ Identification of Pharmacophore.
✓ Improve target interactions (pharmacodynamics).
✓ Improve pharmacokinetic properties.

- Drug development

✓ Patent the drug.
✓ Preclinical studies.
✓ Design and manufacturing which involves chemical and process development.

- ✓ Clinical trial studies.
- ✓ Register and market the drug.
- ✓ Make money.

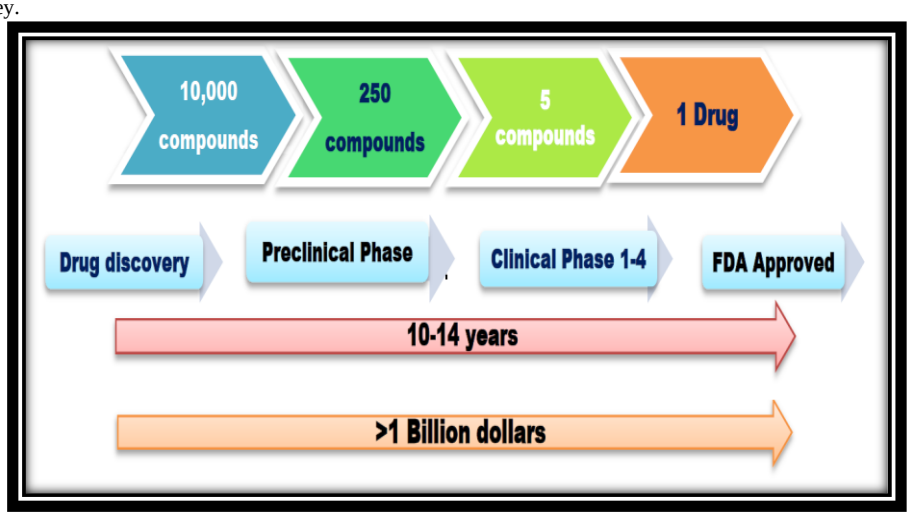


Fig. 1.1: Traditional process of drug discovery and development.

1.4 Computer Aided Drug Design (CADD) and Molecular Docking

Drug discovery and development is a lengthy process which includes searching for promising hits, translating hits to leads, and finally validating leads to drug candidates in clinical trials. Since few decades the investment for the drug discovery and development has considerably increased.
But from the current scenario it was found that the output is hampered by low efficiency and high failure in drug discovery and development process. Computer aided drug design (CADD) is one of the new and most effective method for the drug discovery and save time, money and resources too. **(Fig: 1.2).** It has been seen that by the use of CADD approaches we can reduced the cost of drug discovery and development up to 50%. CADD consist use of any software program based process for establishing a standard to relate activity to structure. The discovery of drugs must have been accidently done when man came into contact with natural herbs.

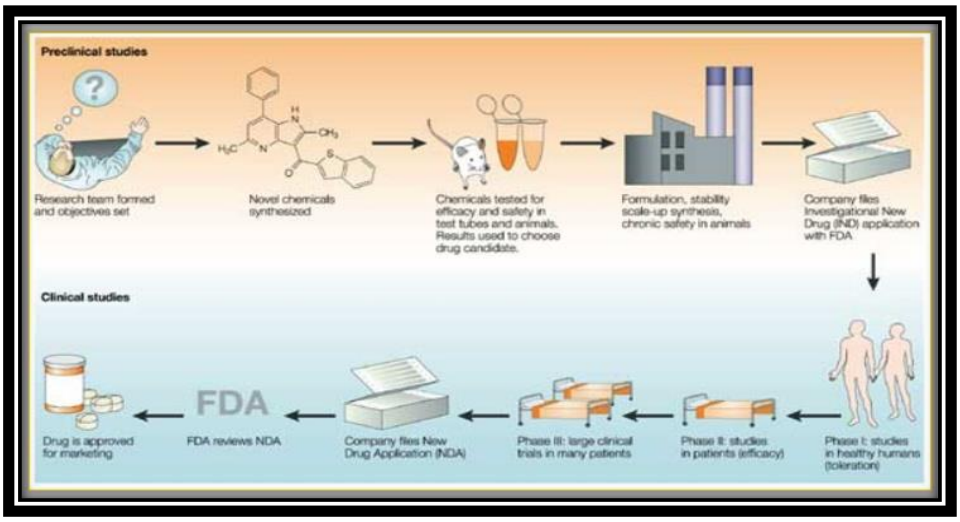


Fig. 1.2: Process of drug discovery and development.

The traditional way to discover new drugs has been to screen a large number of synthetic chemical compounds or natural products for desirable effects. Although this approach for the development of new pharmaceutical agent has been successful in the past. **(Fig: 1.3).**

1.5 Classification of CADD

There are mainly two types of CADD for design of new drug molecules:
1.6.1 Structure Based Drug Design (SBDD) / Direct Design
1.6.2 Ligand Based Drug Design (LBDD) / Indirect Design
The structure based approach uses the 3D structure of receptor or protein serving as target molecule for the screening of the potential ligand molecules followed by synthesis, biological testing and optimization. On the other hand Ligand based drug design involves collecting large number of ligand molecules with diverse structures, known potency and biological activity.

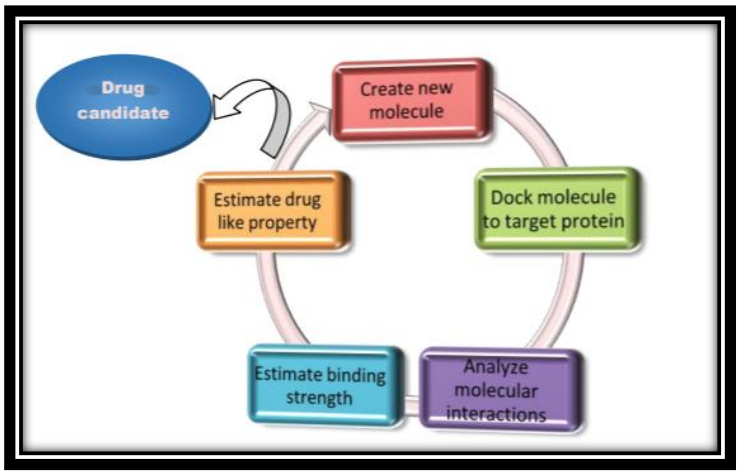


Fig. 1.3: General Principle for Drug design through CADD.

These molecules are then subjected for virtual screening to enhance potency and for identification of new chemical molecules through virtual screening of a large chemical database. Using both the drug design approach produces more effective result than any single approach since both methods are able to complement their strengths and weakness.

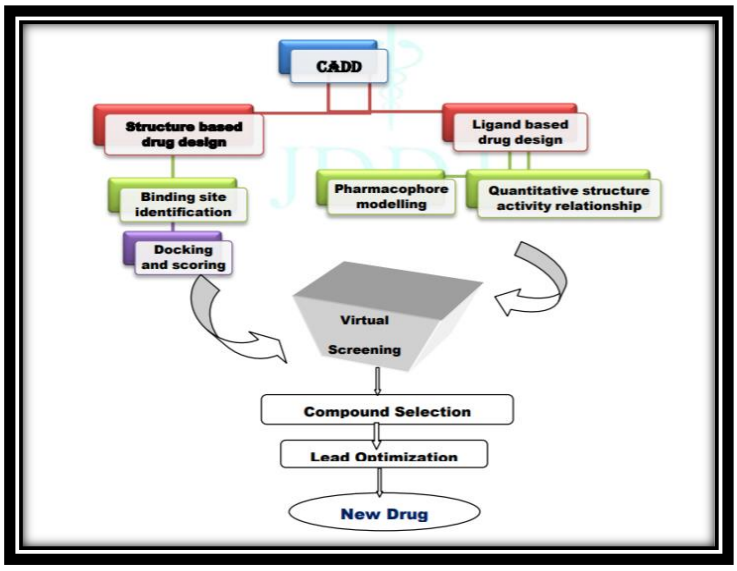


Fig. 1.4: Structure based and Ligand based drug design.

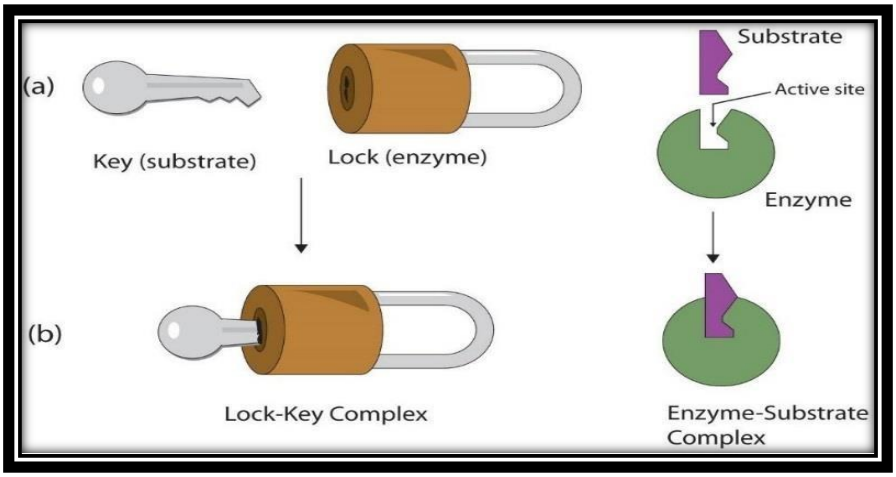


Fig. 1.5: Model of Molecular Docking

Structure based and Ligand based drug design

Drug discovery is the vast field which composed of several disciplines such as chemical and structural biology, computational chemistry, organic synthesis and pharmacology. And accordingly it comprised of various stages which includes:

I. ***Target identification*** includes identification and isolation of single target for the study of function and association with particular disease.

II. ***Target validation*** is the stage where the identified target is correlated with disease of interest. And also involves the understanding of strength to regulate biological function after binding to a native molecule.

III. ***Lead identification*** it is the main step in drug discovery which contributes to synthesis of molecule having high degree of potency, efficacy and specificity against a specific target and also possessing a drug like properties for the cure of disease when intended to the patient.

IV. ***Lead optimization*** covers enhancing potency and other significant properties for the compound to act as suitable candidate for acting as a drug.[33,34]

In discovery and development of the novel drugs CADD is mainly for three major purpose: A) Screening of large compound libraries in to smaller sets of compounds, to experimentally only those compounds possessing higher predicted activity.

B) Instruct the optimization of lead compounds, to improve ADME/T properties.

C) Design the novel compounds either by adding or removing a group or by linking a fragments in to novel compounds.[35,36]

1.8 Advantages of CADD

- In CADD we can reduce the synthetic and biological testing efforts.
- It gives the most promising drug candidate by eliminate the compounds with undesirable properties (poor efficacy, poor ADMET etc.) through in silico filters.
- It is a Cost-effective, time saving, Rapid and automatic process.
- Through it we can know about the drug-receptor interaction pattern.
- It gives compounds with high hit rates through searching huge libraries of compounds in silico in comparison to traditional high throughput screening.
- These approaches minimize chances of failures in the final phase.

Following steps are taken in to consideration for molecular docking study:

1.8.1 Ligand preparation

1.8.2 Protein preparation and its refinement

1.8.3 Receptor grid generation

1.8.4 Protein ligand docking

1.8.1 Ligand preparation

The Schrödinger ligand preparation was done by using LigPrep panel application which consists of series of steps that perform conversion of 2D structures to 3D structure, apply correction to the structure by minimizing the proper bond angles and distances and optimize the structure by minimizing its energy through force-field OPLS3.

1.8.2 Protein Preparation and its Refinement

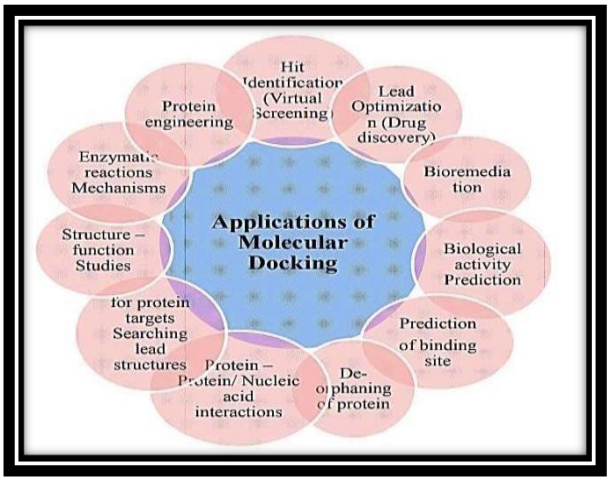
For molecular docking study protein is the essential component and it is necessary to minimize the energy of protein molecule prior to docking studies with ligands. Both the Protein for ligand docking study was prepared by using protein preparation wizard tool in which was used to import proteins for the protein data bank (PDB). Proteins obtained from the PDB, vendors and other sources frequently have missing hydrogen, partial charges, side chain and whole loops region. So, to overcome all these barriers in docking study the proteins to undergone through pre-processing and it was done by selecting following parameters.

- Add hydrogen
- Create zero order bonds to metals
- Create disulphide bonds
- Filling missing side chains using prime
- Fill in missing loops using prime
- Delete water beyond 5.00 Å From het group
- Generate het state using Epik: PH 7.0+/- 2.0

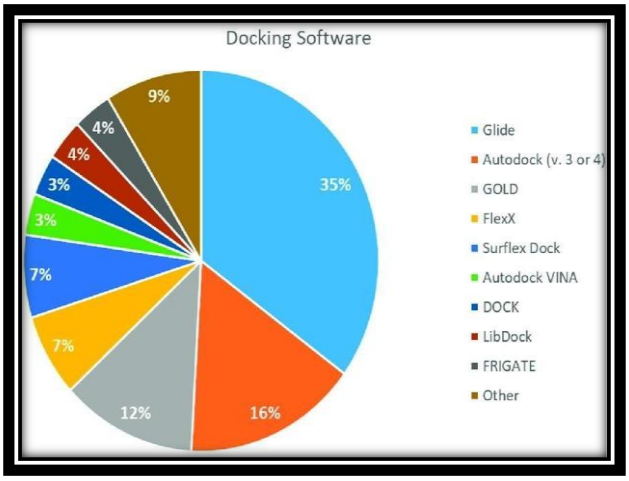
1.8.3 Receptor grid generation

Grid generation must be performed prior to running a virtual screen with glide. The shape and properties of the receptor are represented in a grid by field that provides progressively more accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, Glide prepares grids for each conformation, to ensure that possible actives are not missed.

Applications of Molecular Docking.



Software's used for Molecular Docking



RESULT AND DISCUSSION :

Molecular docking has proven to be a powerful tool in modern drug discovery, offering medicinal chemists a cost-effective and time-saving method to visualize molecular interactions. By accurately predicting how ligands bind to target receptors, docking aids in the design and development of novel drugs. This computational approach supports the discovery of new therapeutic options by identifying potential drug candidates from large databases of molecular structures. Additionally, it provides essential structural insights, enhancing researchers' understanding of drug-receptor interactions.

One of the key advantages of molecular docking is its ability to address urgent health challenges, such as malaria, heart failure, cancer, and other infectious diseases. The rise of drug-resistant strains has created an urgent need for new and effective treatments. Molecular docking, combined with other computational drug design methods, facilitates the rapid and economical exploration of novel therapies, potentially offering new remedies for resistant diseases.

Molecular docking also supports drug repurposing—finding new therapeutic uses for existing drugs. This approach can speed up drug discovery and lower costs compared to traditional methods, as these compounds have already been validated for safety. Moreover, the optimization of lead compounds and evaluation of biological pathways through docking enable researchers to refine drug candidates for improved efficacy and safety.

CONCLUSION :

Computer-Aided Drug Design (CADD) has emerged as a transformative tool in drug discovery, widely adopted in both academic research and the pharmaceutical industry. Through molecular docking, a core technique of CADD, researchers can accurately predict the binding interactions between potential drug molecules (ligands) and their target proteins. By analyzing 3D molecular structures and calculating docking scores, CADD aids in identifying and optimizing promising drug candidates, streamlining the drug development process. Despite certain complexities, such as the optimization of lead compounds and evaluation of biological pathways, CADD's ability to conduct virtual screenings and optimize drug-target interactions makes it a valuable, cost-effective, and efficient approach. The ongoing advancements in molecular docking and CADD continue to enhance drug discovery, offering a powerful pathway for the development of innovative and effective therapies.

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