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Computer aided drugs design

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Abstract-

Discovery and development of a new drug is generally known as a very complex process which takes a lot of time and resources. So now a day's computer aided drug design approaches are used very widely to increase the efficiency of the drug discovery and development course. Various approaches of CADD are evaluated as promising techniques according to their need, in between all these structure-based drug design and ligand-based drug design approaches are known as very efficient and powerful techniques in drug discovery and development. These both methods can be applied with molecular docking to virtual screening for lead identification and optimization. In the recent times computational tools are widely used in pharmaceutical industries and research areas to improve effectiveness and efficacy of drug discovery and development pipeline. In this article we give an overview of computational approaches, which is inventive process of finding novel leads and aid in the process of drug discovery and development research.

Keywords-CADD: Introduction, Various approaches of applied in CADD, Virtual screening, Molecular Docking, Pharmacophore Modeling, Successful CADD Approches to the Treatment of Neurodegenerative Disorder.

Introduction-

To introduce a new drug to the market is a costly affair that involves considerable time and money. The average time taken to discover/develop a drug is around 10-15 years and the cost stands at around US$ 800 million[1]. A combination of advanced computational techniques, biological science, and chemical synthesis was introduced to facilitate the discovery process, and this combinational approach enhanced the scale of discovery. Eventually, the term computer-aided drug design (CADD) was adopted for the use of computers in drug discovery[2]. Advanced computational applications have been shown to be effective tools and notable successes have been achieved using these techniques.

CADD is a specialized discipline, whereby different computational methods are used to simulate interactions between receptors and drugs in order to determine binding affinities[3]. However, the technique is not limited to studies of chemical interactions and binding affinity predictions, as it has many more applications ranging from the design of compounds with desired physiochemical properties to the management of digital repositories of compounds. An overview of CADD is provided in Fig.1. CADD may be broadly categorized embracing both structure-based and ligand-based drug design. Fig- 2 illustrates various approaches applied in CADD.

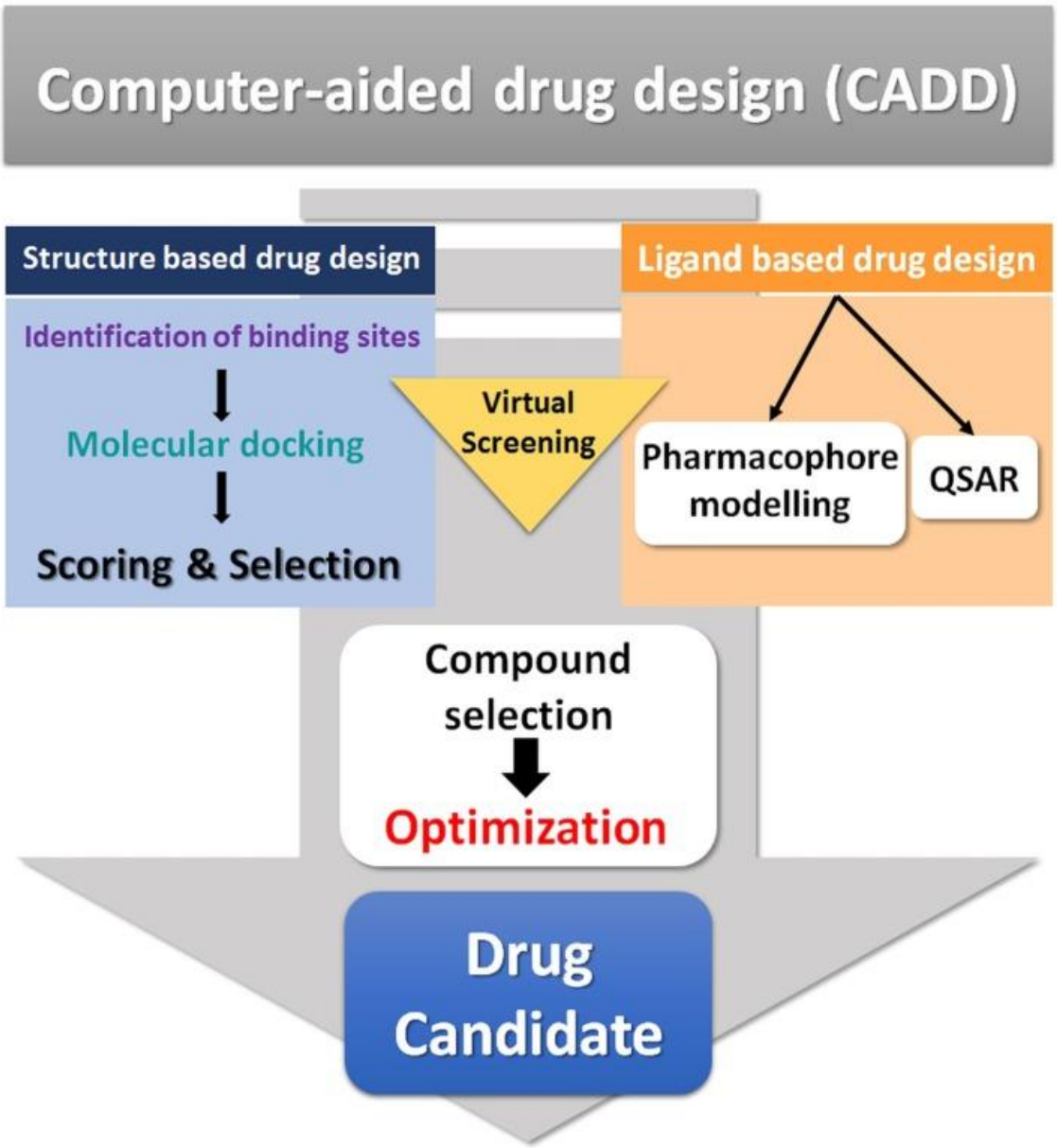

Fig. 1 overview of CADD process.

Various approaches of applied in CADD-

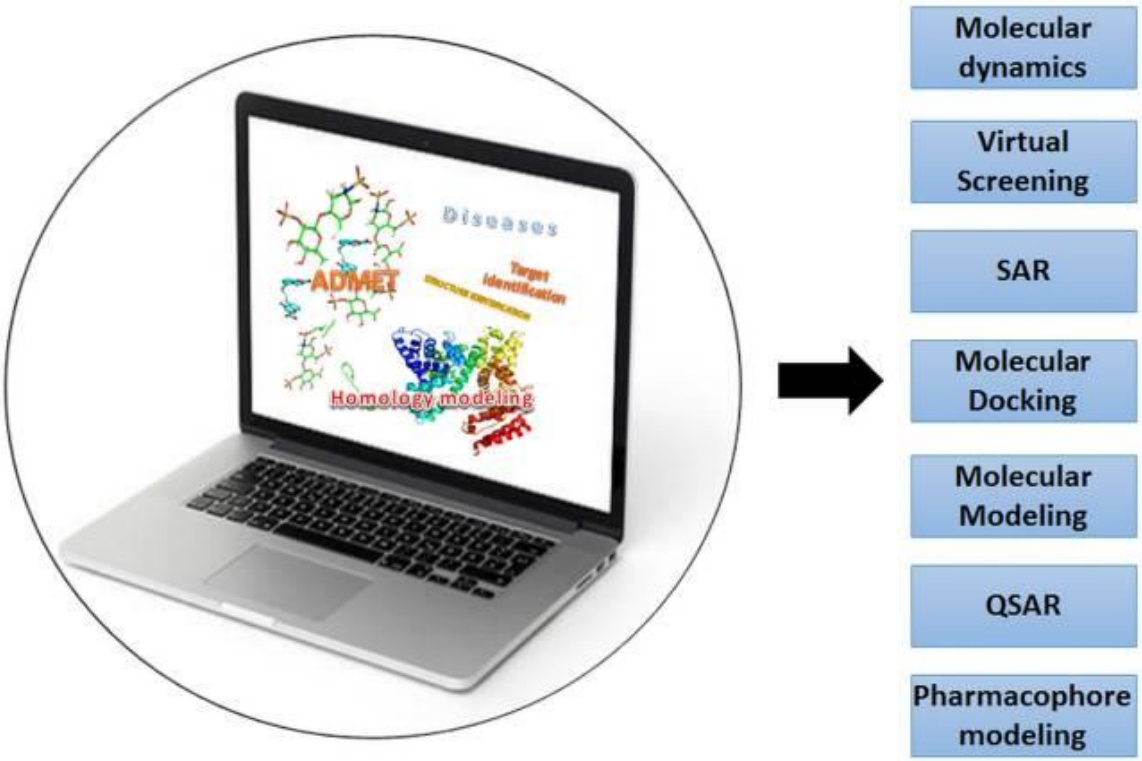

Fig. 2- Various approaches computer aided drug design.

Virtual screening-

Virual screening has been worked as a most convenient tool now a day to find out the most favorable bioactive compounds with the help of information about the protein target or known active ligands. In the recent time virtual screening is known as a mind blowing alternative of high-throughput screening mainly in terms of cost effectiveness and probability of finding most appropriate novel hit through filter the large of libraries of compounds[4]. The primary technique for identifying new lead compounds in drug discovery is to physically screen large chemical libraries for biological targets. In experiments, high-throughput screening identifies active molecules by performing separate biochemical analysis of more than one million compounds. However, this technology involves significant costs and time. Therefore, a cheaper and more efficient calculation method came into beinvg, namely, virtual high-throughput screening. The method has been widely used in the early development of new drug. The main purpose is to determine the novel active small molecule structure from the large compound libraries. It is consistent with the purpose of high-throughput screening. The difference is that virtual screening can save a lot of experimental costs by significantly reducing the number of compounds for the measurement of the pharmacological activity, while high-throughput screening needs to perform experiments with all compounds in the database. Here, we will discuss common methods of virtual screening.

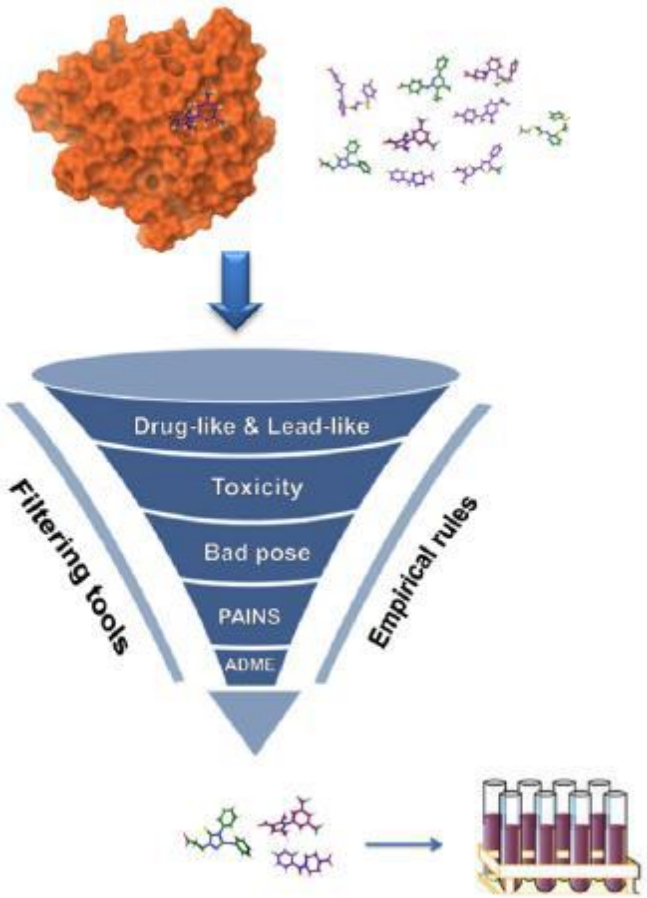

Fig: Overview of Virtual screening process.

Molecular Docking-

In general, the structure of small molecules can be freely changed, while macromolecules remain rigid or retainsome of the rotatable amino acid residues to ensure computational efficiency. In flexible docking, the simulated system conformation is free to change, thus consuming more computing resources while improving accuracy. What's more, the establishment of binding sites in molecular docking methods is very important. For the first time, Collins successfully determined the binding sites on the surface of proteins using a multi-scale algorithm and performed flexible docking of molecules, which greatly promoted the development of molecular docking. An ideal search algorithm should be fast and effective, and the scoring function must be capable of determining the physicochemical properties of molecules and the thermodynamics of interactions. The search algorithm is responsible for searching different poses and conformations of a ligand within a given target protein and the scoring function estimates the binding affinities of generated poses, ranks them, and identifies the most favorable receptor/ligand binding modes[5-6].

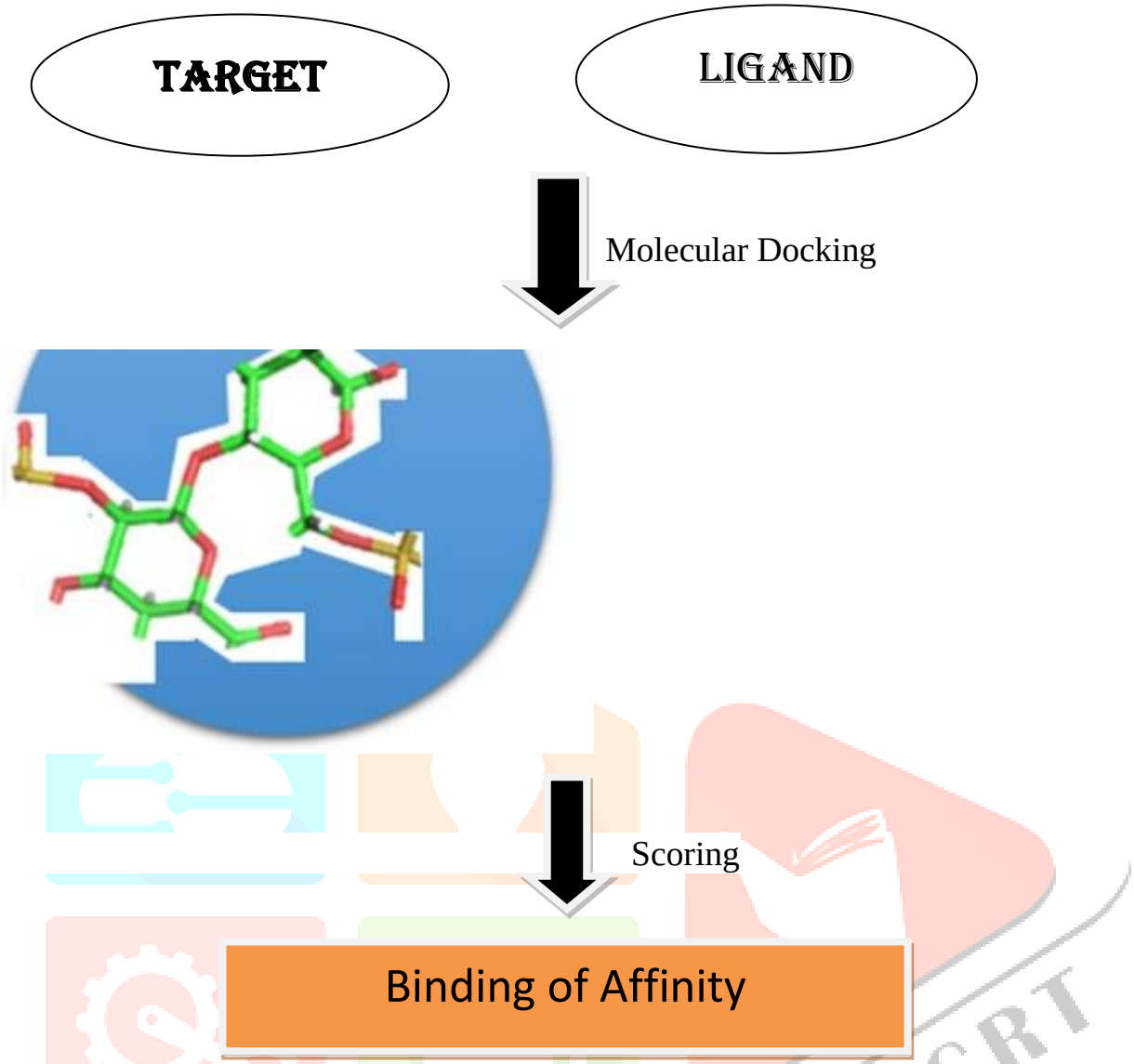

Fig. Estimation principle of molecular docking.

List of major available molecular docking tools-

3.	Glide	Paid	Monte Carlo
4.	FlexX	Paid	Incremental construction
5.	Dock	Freely available	Shape fitting (sphere sets)
6.	LigandFit	Paid	Monte Carlo
7.	FRED	Freely available	Shape fitting (Gaussian)
8.	ICM	Paid	Monte Carlo
9.	eHiTS	Paid	Incremental construction
10.	Surflex-Dock	Paid	Incremental construction

Pharmacophore Modeling-

There are two main methods for the identification of pharmacophores. On one hand, if the target structure is available, the possible pharmacophore structure can be inferred by analyzing the action mode of receptor and drug molecule. On the other hand, when the structure of the target is unknown or the action mechanism is still unclear, a series of compounds will be studied for pharmacophores, and information on some groups that play a key role in the activity of compound will be summarized by means of conformational analysis and molecular folding[11]. Active compound that is suitable for constructing the model will be selected in the pharmacophore recognition process. Then, conformation analysis is used to find the binding conformation of molecule, and to determine the pharmacophore. In recent years, with the development of compound databases and computer technology, the virtual screening of databases using the pharmacophore model has been widely used, and has become one of the important means to discover lead compounds[12]. The elucidation of common pharmacophore features is conducted by aligning conformational models and active compounds three dimensionally. A superimposition algorithm assembles training set compounds (3D structure) in the same position/arrangement of their respective chemical properties/features. Pharmacophoric features are positioned such that all/maximum compounds share a common chemical functionality. To refine a shared pharmacophore feature, information regarding inactive compounds can be included in the model generation process. A number of tools and software have been developed for pharmacophore development, such as, Phase, Catalyst/Discovery Studio, MOE, and LigandScout[13].

Quantitative Structure–Activity Relationship (QSAR)-

The case of unknown receptor structure, the QSAR method is the most accurate and effective method for drug design. Drug discovery often involves the use of QSAR to identify chemical structures that could have good inhibitory effects on specific targets and have low toxicity (non-specific activity). With the further development of structure–activity relationship theory and statistical methods, in the 1980s, 3D structural information was introduced into the QSAR method, namely 3D-QSAR. Since 1990s, with the improvement of computing power and the accurate determination of 3D structure of many biomacromolecules, structure-based drug design has gradually replaced the dominant position of quantitative structure-activity relationship in the field of drug design, but QSAR with the advantages of small amount of calculation and good predictive ability. the classical QSAR, the QM calculations use reactivity descriptors in ligand-based QSARs, which provides an implicit model and calculate an exact enthalpy contributions of protein-ligand interactions. However, for the ab initio fragment, molecular orbital calculation in the structure-based QSARs, which obtains an explicit model and a clear enthalpy, changes the binding energy in different additional conditions. Moreover, it also calculates the free energy contribution of ligand-target complexes formation in structure-based and ligand-based QSAR models. Using a large number of ligand-target complexes to discuss the change of their binding affinity, more accurate optimization steps can be conducted based on good prediction and interpretation models. Then, the structures of new compounds are predicted and optimized. In short, 3D-QSAR is actually a research method combining QSAR with computational chemistry and molecular graphics. It is a powerful tool for studying the interactions between drugs and target macromolecules, speculating the image of simulated targets, establishing the relationship of drug structure activity, and designing drugs[14].

SUCCESSFUL CADD APPROACHES TO THE TREATMENT OF NEURODEGENERATIVE DISORDERS –

The success of CADD has resulted in its being recognized as an important technique in the research and pharmaceutical fields. There are many examples of the successful application of CADD, but here we describe its successes with respect to the design of drugs for the treatment of NDs. Amyloid-β is an important therapeutic target in Alzheimer's disease. Chen *et al*. used an *in silico* approach to study a series of peptides against the fibrillar form of Aβ, and reported two highly active compounds. These peptides were subsequently found to inhibit the neurotoxic effects of Aβ on neuroblastoma cells[15].

ADVANTAGES OF CADD-

1. Through it we can reduce the synthetic and biological testing efforts.
2. It gives the most promising drug candidate by eliminate the compounds with undesirable properties (poor efficacy, poor ADMET etc.) through **in silico** filters.
3. It is a Cost-effective, time saving, Rapid and automatic process.
4. Through it we can know about the drug-receptor interaction pattern.

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