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APPROACHES IN COMPUTER AIDED DRUG DESIGN IN DRUG DISCOVERY

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Abstract

The process of identifying and producing a novel drug is frequently viewed as a time consuming and costly. As a result, computer-aided drug design technology is increasingly being used to increase the efficiency of the drug discovery and development process. Various CADD approaches are viewed as promising techniques based on their demands; nevertheless, structure-based drug design and ligand-based drug design approaches are well-known as highly efficient and powerful drug discovery and development strategies. Both methods can be used with molecular docking to do virtual screening for the purpose of discovering and optimizing leads. Computational tools have grown in popularity in pharmaceutical industry and academic sectors in recent years as a means of boosting efficiency and effectiveness of the drug discovery and development pipeline. In this piece, we will look at computational approaches, which offer a novel approach to finding new leads and assisting in drug discovery and development research.

Keywords **-computer aided drug design [CADD], Structure based drug design [SBDD], Ligand based drug design [LBDD], Pharmacophore, Virtual screening, Molecular docking, QSAR, Database.**

I. INTRODUCTION

The computational approaches in drug design, discovery and development process gaining very rapid exploration, implementation and admiration. A novel drugs introduction to market is an extremely difficult, risky, and expensive procedure in term of resources [time, money, labor]. In general, the process of discovering new drugs and developing them requires 10 to 14 years and total investment of more than 1 billion. Computer aided drug design [CADD] is a popular new drug design strategy since it helps reduce time, cost, and risk related issue. There is evidence that using CADD methods can reduce the cost of drug discovery and development by upto 50%. Any software-based technique is used in CADD to build a standard for connecting activity to structure. (Surbhi, Bk Singh)

The goal of computer aided drug design [CADD] which combines several chemical molecular and combined technique, is to find, design, and create therapeutic chemical agents. Structural activity relationships [SAR] are the foundation of several CADD methodologies. The primary goals of CADD are part of multidisciplinary effort to enhance bioactive chemicals, provide therapeutic alternatives, and comprehend molecularly based biological activities. (Antoine Daina, Marie-Claude Blatter)

The primary benefit of adopting CADD methods is the selection of the compounds for biological assays following a reasonable screening process that was directed by a target or a database of ligands. If the molecule appears promising as a possible drug, this strategy seeks to minimize the number of tested analogues, stimulated by computer software. (Nascimentol, Thiago Mendonca)

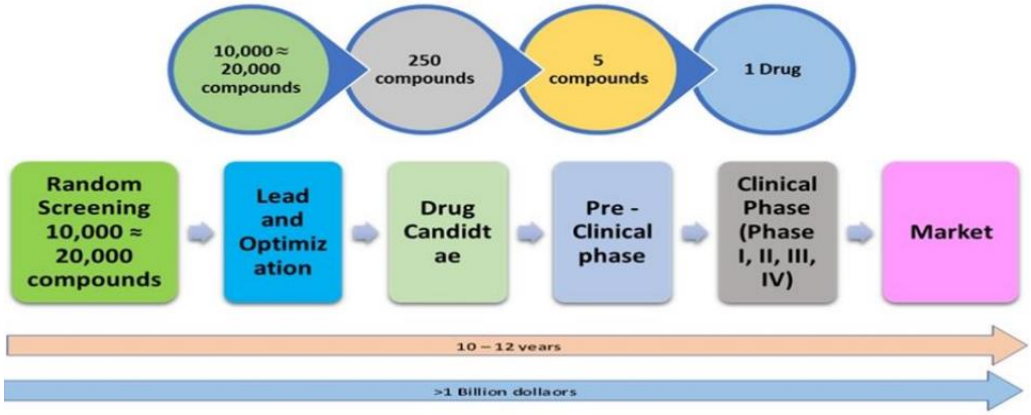

Fig.1 Traditional drug research and development procedure

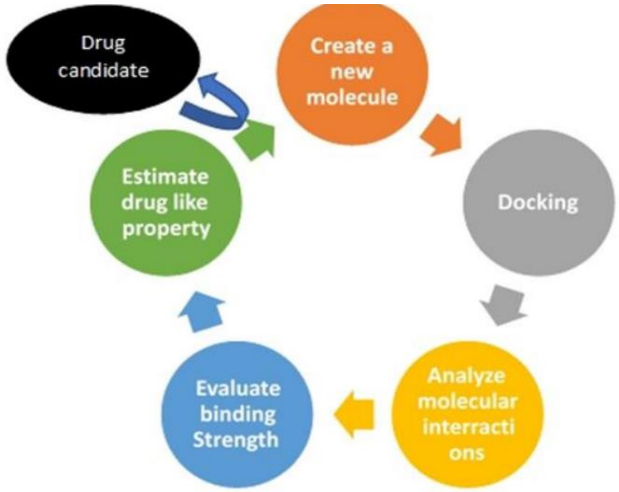

Fig.2 General principle for drug design through CADD

There are mainly two types of approaches for drug design through CADD is the following:

1. Structure based drug design.
2. Ligand based drug design. (Dan Vasilescu)

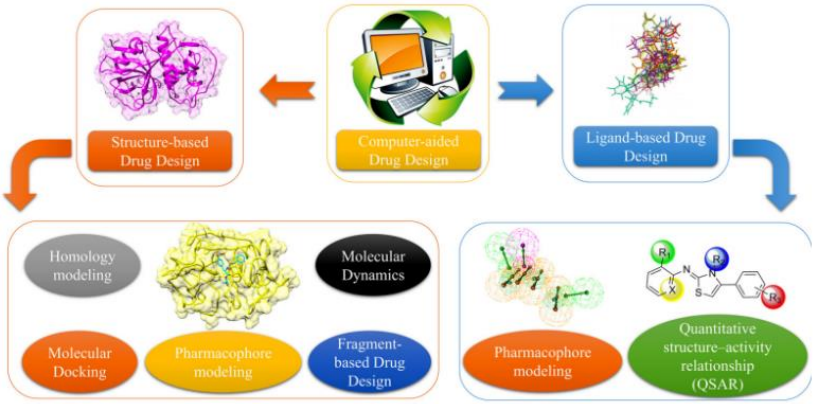

Fig.3 The main approaches in CADD method

Structure based drug design.

Structure based drug design has played an important role in drug discovery and drug development. This approach requires the understanding of receptor-ligand interaction. In this event that the target 3D structure is known, it can be utilized for the plan of modern ligands. The basic data is either from X-ray crystallography, NMR, or from homology modelling. The role of SBDD techniques is to assess complementarities and forecast potential binding affinities and modes between small compounds and their macromolecular receptors. The effectiveness of SBDD has a long history, and computational approaches differ greatly in terms of methodology, efficiency, and speed. While some can provide precise binging modes, others are better suited for quick searches of large datasets. (Shuxing Zhang)

The continuous collection of knowledge that makes up SBDD is a cyclic process. to find possible ligands, in silico investigations are carried out starting with a known target structure. The most promising molecules are synthesized after these molecular modelling approaches. Then utilizing a verity of experimental platforms, evaluations of biological

parameters such as potency, affinity, and efficacy are continued. The three- dimensional structure of the ligand -receptor complex can be solved, provided that active substances are found. Because of the available structure are found. Because of available structure, it is possible to see several intermolecular characteristics that aid in molecular recognition. For the examination of binding conformation of important intermolecular interactions, identification of unknown binding sites, mechanistic studies, and the clarification of ligand-induced conformation changes, structural descriptions of ligand-receptor complexes are helpful. (Lenardo G. Ferreia)

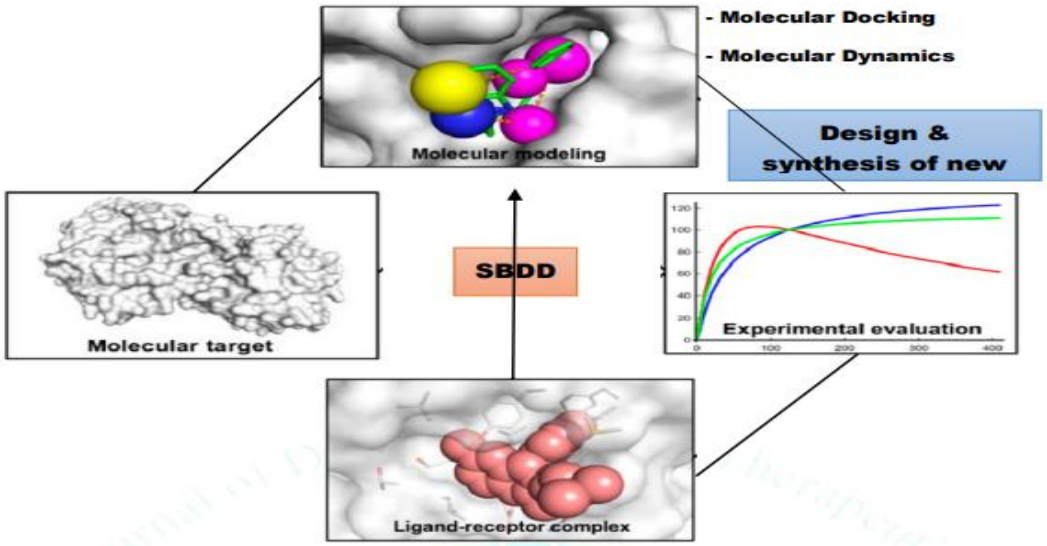

Fig.4 Outline of SBDD

Ligand based drug design

Lead optimisation and identification in the absence of the receptor 3D information are largely dependent on the availability of pharmacologically useful compounds and their bioactivities. Data mining, QSAR, and pharmacophore modelling are some of the computational techniques. (Shuxing Zhang)

Ligand based drug design is also known as indirect drug design, is dependent on knowledge of other active compounds that could block desired biological targets. These well-known compounds serve as the basis for pharmacophore models, which defines the structural features required for binding to the biological target. As an alternative, we can assess the association between a compound computed molecular characteristics and its experimentally determined biological activity using the quantitative structural activity relationship. The activity of novel analog may be predicted using these predicted OSAR correlations. (Mohammad Hassan Baig, Khurshid Ahmad)

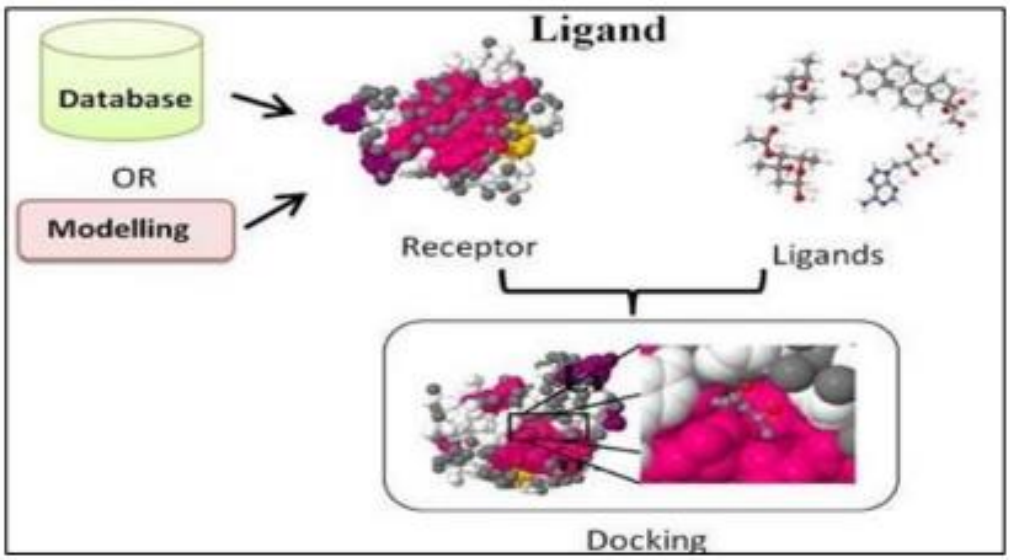

Fig.5 Outline of process involved in LBDD

II. MOLECULAR DOCKING

When one molecule connects with a second molecule (which might be a protein or ligand molecule) to form a stable complex structure, we can predict their preferred orientation using a technique called molecular docking. Docking occurs when a ligand binds to its target protein or receptor. By examining and stimulating the interaction between drug molecules and target receptors molecules, molecular docking is mostly used to predict stable drug interactions. They are employed to create various ligand conformations and orientations, and the best one is chosen for study.

Deep insight into the different sorts of interactions between a ligand and a macromolecule, particularly a protein is often provided by docking studies. Currently, there are novel, computationally demanding techniques that help us to learn the microenvironment as it interacts with the presence or absence of water molecules. The enhanced processing possibilities have also boosted flexibility. Along with small molecular docking protein-protein interactions, protein DNA interactions or protein RNA interactions can also be examined depending on the specific cellular level complexities involved.

There are several molecular docking tools available that includes AutoDock, FRED, Ehits, and FTDock etc. (Maithri G, Manasa B Vani SS,)

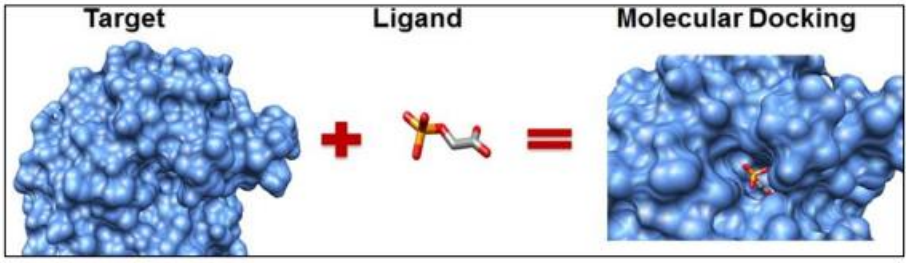

Fig.6 Molecular docking process

III. VIRTUAL SCREENING

Virtual screening is the process of rating and ranking compounds in huge chemical libraries based on how likely they are to have an affinity for a certain target. This is because virtual screening may be seen an effort to expand QSAR concept along the chemical dimension defined by currently synthesized molecules as well as conceivably synthesizable molecules. QSAR was originally focused on tiny sets of congeneric drugs. The phrase was first used in the late 1990, when computer-based approaches had developed to the point of maturity to provide a substitute for experimental high throughput screening procedures, which had shockingly subpar results and higher cost than expected. Since the pharmaceutical industry has grown to recognize virtual screening approaches as an effective supplement to HTS over time, they are unquestionably now a necessary component of the lead generation process. (S.Ekins, Mestres)

Virtual screening is mainly categorized in two types, that are.

1. Structure based virtual screening.
2. Ligand based virtual screening.
3.

Structure based virtual screening

Target and database preparation, docking and post docking analysis, and compound prioritization for biological testing are all include in structure based virtual screening process. In circumstances where the target proteins 3D structure is known, structure based virtual screening is used. (Mohammad Hassan Baig, Khurshid Ahmad)

Ligand based virtual screening.

The similarity principle, which posits that comparable substances have similar biological effects, is the foundation for ligand-based virtual screening. These ideas rely on one or a small number of empirically discovered hits. The identification of new potentially active compounds results from the effective searching of large ligand libraries for substances with chemical properties that are comparable to those of the known actives. The measure of similarity used. Which can range from two dimensional descriptors, such as fingerprints, to shape comparisons and three-dimensional descriptors, such as employing pharmacophores, is the main distinction between the various ligand based virtual screening approaches. (Markus Lill)

IV. PHARMACOPHORE MODELLING AND MAPPING

A pharmacophore is a molecular framework that describes the key properties that give a molecule its biological activity. Pharmacophore models can be created utilizing the structural traits of active ligands that binds to the drug target when structural knowledge about the drug target is sparse. (Syed Sarim Imam and Sadaf Jamal Gilini)

Stages involved in building a pharmacophore model can be summarized as follows. (Sumudu P. Leelanandaand, Steffen Lindert)

Literature or database search is used to find the active substances that are known to the targeted receptor.

Essential atom types and their connectivity are established for 2D pharmacophore models. For 3D pharmacophore modelling, conformations are defined using IUPAC nomenclature.

Ligand alignment is utilized to identify essential characteristics for binders.

Creating pharmacophore models.

Ranking pharmacophore models are choosing the top models.

Pharmacophore model validation.

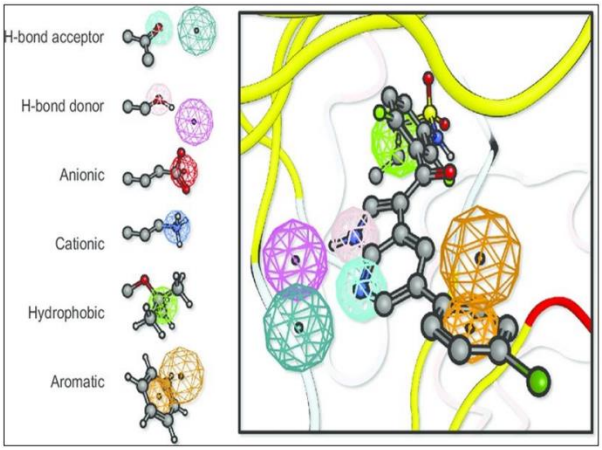

Fig7. Overview of pharmacophore mapping.

V. QSAR

When structure-based techniques are not appropriate since it is unknown what the structure of the target macromolecule is, the QSAR technique frequently used. (Surabhil, B.K. Singh)

Using mathematical models, the "quantitative structural-activity relationship" (QSAR) technique connects chemical structure to biological or chemical activity. (Emilio Xavier Esposito, Anton J. Hopfinger and Jeffry D. Madura) An explanation of this relationship can be created using a model that is built using the activity of a group of ligands. The QSAR model enables one to determine the impact of a specific attribute on the activity of a molecule, as opposed to a pharmacophore model, which simply encodes the fundamental characteristics of an active ligand. For instance, the QSAR model can show that a property has a strongly negative or weakly positive impact on ligand activity. A pharmacophore model is not capable of providing this information. In modeling process, its crucial to quantify a ligands structure and activity. Since a structure cannot be merely quantified by a value, quantifying a structure is not an easy task. Instead, a collection of characteristics often referred to as the "descriptors" is calculated from the structure and utilized to quantify it. Structure descriptors can be used as independent variables, and activity can be used as a dependent variable, to create a model that illustrates how the two are related. After a QSAR model is build and validated, it can predict biological activity of novel molecule from their structural properties. (ROGER PERKINS, HONG FANG, WEIDA TONG)

VI. DATABASE IN COMPUTER AIDED DRUG DESIGN

In computing, a database is a structured collection of data that is electronically stored and accessed. Small database can be stored and accessed. Small databases can be stored on a file system, whereas large databases are hosted on computer clusters or cloud storage. (Darshana M. Nagare, Arti M. Jadhav) To make opinion about target selection, lead discovery, lead optimization, and candidate selection, researchers in big pharmaceutical companies often rely on variety of data resource and technologies. A position of this data is either generated internally or licensed from business that profitable. The various types of databases have evolved along with database technology over time. There are currently many distinct sorts of databases, and each has advantages and disadvantages depending on how it was created. (Shyam Narayan Gupta, Piyush Yadav, Manoj Kumar Yadav)

Bioinformatics

Any application of computers to manage biological data is referred to as bioinformatics. Most people adopt a more limited definition of bioinformatics, which they refer to as "computational molecular biology"-the use of computer in the field of biology, computer science, and information technology. It involves the use of computer to gather, manage, and analyze biological data. (Pragya Yadav, Manoj Kumar Yadav, Piyush Yadav)

Types of databases in bioinformatics: -

1. chemical database
2. biochemical database
3. ADMET database

Chemical database

A database created expressly to store information about chemical is known as chemical database. This data includes information on spectra, reactions and synthesis, chemical and crystal structures, and thermophysical data. Chemical structures are typically depicted on paper using lines that represent the chemical links between the atoms. These visual representations are perfect foe chemists, but they are not appropriate for computational use, especially for search and

storage. Lists of atoms and their connections are typically used to represent small compounds like ligand. Using the sequences of their amino acid building components, however, allows for a more compact representation of large compounds like proteins. Terabytes of physical memory will be required to store and search information on millions of molecules in large chemical database of structures.

Chemist can search databases based on characteristics, sections of the structures, and the IUPAC designations of the compounds. The support for sub-structured search that chemical databases offer sets them apart from other general-purpose databases. All characteristics of molecules other than their structure can be divided into physiochemical or pharmacological characteristics, often known as descriptors. Database management programmed used to keep distinct records on chemical substance are known as registration systems. These are frequently employed in industrial databases, patent management programs and chemical indexing. (Shyam Narayan Yadav, Piyush Yadav Manoj Kumar Yadav)

ADME database

In the broadest definition, is a well-organized collection of data. It is an electronic system that makes it simple to access, modify, and update data. Many businesses utilize databases to store, manage, and retrieve information. Database management system are used to manage contemporary databases. Because these features account for around 60% of all medication failures in clinical trials, predicting ADME properties is crucial for the drug design process. In contrast to the past, when ADME approaches were applies towards the end of drug development process, they are now applied early in the process to weed out compounds with poor ADME features, resulting in significant and development cost reductions. Update and through information on how chemicals interact with drug metabolizing enzymes and drug transporters is also available in the ADME database. It is designed to be used in drug research and development, including ADME investigations and drug-drug interactions. Information is given according to category, drug name, enzyme, reaction, and kind. Chemical and metabolite structures, as well as kinetic value mentioned in the literature, support it.

More than 26000 chemicals, including natural product and preparations, as well as other elements influencing the action of drug metabolizing enzymes, are all included in the ADME database. The information gathered from almost 18000 citations. (Pragya Yadav, Manoj Kumar Yadav, Piyush Yadav)

Biochemical database

Genome sequencing of humans and other model organisms has generated enormous volumes of data that are pertinent to the study of human disease. As global repository for nucleotide sequences of various sources, the international collaboration GenBank, DNA Data Bank of Japan (DDBJ), and European Molecular Biology Laboratory (EMBL) are also useful. Everyday, the three databases synchronize their records. Comprehensive and properly annotated information on protein sequences and functions is available from Swiss-Prot and Protein Information Resource (PIR). Swiss-Prot now has 410 518 protein sequence in its database. All translations of EMBL nucleotide sequences that are not already present in the database are included in translated EMBL, a computer-annotated protein sequence database supplement of Swiss-Prot. The only global repository for the structural information of biological macromolecules is the Protein Data Bank (PDB). (Chun Meng Song, Shen Jean Lim and Joo ChuanTong)

VII. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION AND TOXICITY (ADMET)

The requirement to identify the ADMET characteristics of lead during the initial stages of drug screening resulted from high attrition rates brought on by subpar pharmacokinetic profiles. However, from a time and resource standpoint, it is not practical to experimentally evaluate the pharmacokinetic characteristics of millions of different substances. Thus, virtual screening can be used to filter hits and exclude compounds with undesirable properties in order to swiftly assess the drug likeness of a lead compound prior to through experimental testing. In silico ADMET filters, which are used to predict drug like properties of the substance, are derived from chemical or molecular descriptors similarly to QSAR. The Lipinski rule of five, the rule of three for fragments, and the Veber rules are among the most basic and well-known models. A big chemical database or a list of prospective leads can be filtered using freely accessible web servers like chembioserver and free ADMET filtering-drug. (Stephani Joy Y. Macalinol)

VIII. TOXICITY

Toxicology, which is the extent to which a substance might harm an organism or a component of the body, such as cells or organs, continues to be one of the leading causes of late-stage drug development failure. Early detection of severe toxicity during drug development is crucial to avoid wasting time and money on late stages. Early-stage high-throughput toxicity prediction techniques have recently become available, improving the yield ratio of latter drug development phases. For early-stage prediction and decision-making, there are certain integrated technologies that provide all-sided prediction. DEREK, which was the first program to forecast toxicity, is an example of a conventional

knowledge-based expert system that is based on the expertise of toxicologists as well as data from the literature. Tox alerts is a web server that provides structural alerts for potentially harmful toxic compounds, and its database is open and extendable. To evaluate different toxicity measures, TOPKAT uses cross-validated QSTR models; each module is made up of a unique database. MCASE uses a machine learning approach to find molecular fragments that have a strong likelihood of being connected to the activity that is being observed. Although in silico toxicity models are useful for drug development, more work is still required to increase their predictability and ease of understanding of underlaying mechanisms. (Yulan Wang, Jing Xing)

IX. ADVANTAGES OF CADD

1.reducing the quantity of synthetic and biological tests we conduct can help us save time and money.
2.By removing compounds with unfavorable traits using in silico filters, it determines the most promising treatment candidate.
3. It is simple, quick, and time consuming.
4. It teaches us about the pattern of drug-receptor interaction.
5. By examining enormous libraries of compound in silico, it gives molecules with high success rates when compared to conventional high throughput screening.
6. These techniques lessen the possibility of failures during the final stage. (Surabhi, B.K Singh)

X. CONCLUSION

Using computer aided drug design, we may quickly and cheaply identify the most promising drug candidates in the field of drug discovery and development. It consistently offers hope for advancement in the field of medication discovery. Because so many excellent studies have been completed in recent years using computer aided drug design, it will be crucial soon. With the advancements made to date, computer aided drug design has a bright future in helping to find many more curatives.

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