Review Article

COMPUTER AIDED DRUG DESIGN: A REVIEW

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ABSTRACT

Once upon a time, the method of drug discovery and development was considered as very difficult and time taking but with the modernisation of computational tools and methods, it's been accelerated. CADD (computer aided drug design) is really a very powerful tool nowadays due to its usefulness in making various processes easier and faster. Among various approaches of CADD structure-based drug design and ligand-based drug design approaches are known to be very efficient techniques in drug discovery and development. The foremost fundamental goal in drug design is to predict whether a given molecule will bind to a target or not and even if it does so, then how strongly. In this review article, I even have given a summary of computational approaches, which is creative process of finding novel leads and aid within the process of drug discovery and development research. This review is open for corrections and updates.

1. INTRODUCTION

Drug design, often called as rational drug design, is one of the inventive and innovative processes for finding new medications and drugs supported by the knowledge of biological target. The drug is usually an organic small molecule that activates or inhibits the function of a biomolecule like a protein, lipids, etc which successively leads to therapeutic benefit to the patient. [1]

Computer aided drug design (CADD) provides many measures and techniques that help us in various stages of drug design and thus they reduce the value of research and development time of the drug. It's a posh and highly risky process and therefore the cost and time investment are high during the various phases of drug discovery and development ranging from therapeutic target identification, candidate drug discovery drug optimisation through preclinical and extensive clinical experiments to assess the effectiveness and safety of newly developed drugs. The theoretical tools include empirical molecular mechanics, quantum physics and, more recently, physics. [1]

1.1 Factors affecting drug discovery

(a) Medicinal requirements

(b) Screening facilities

(c) Drug development facilities

(d) Expenses of drug development process

There are various parameters which are to be considered in the designing of drugs; that is the drug should be:

(a) Safe and effective

(b) Bioavailable

(c) Metabolically stable

(d) Minimal side effects

(e) Selective target tissue distribution [2]

1.2 In silico Drug Discovery Process consists of three Stages:

Stage 1: Therapeutic target are identified and small compounds library are generated.

Stage 2: Interaction testing of selected hits by docking at the binding sites.

Stage 3: Selected compounds are subjected to pharmacokinetic studies and therefore the compound that passes these parameters is employed as a lead compound [2]

1.3 In silico ADMET prediction models

The interaction between drugs and physical body may be a bidirectional process. Drug produce effect in physical body, undergoes absorption, distribution, metabolism & excretion.[3]

To look at the atomic highlights that impact the absorption, distribution, metabolism, excretion and toxicity (ADMET) of medicine, QSAR strategies and related approaches are utilized. Because the three-dimensional structures of a couple of major ADMET proteins are accessible, structure-based (docking-scoring) computations are administered to enrich or to travel past QSAR studies. [4]

Virtual screening of photochemical was performed through atomic docking in silico ADMET and drug-likeness forecast to differentiate the potential hits which will repress the impacts of SARS-CoV-2. The in silico computational comes about uncovered that the photochemical like glycyrrhizin corrosive, limonin, 7-deacetyl-7-benzoylgedunin, maslinic corrosive, corosolic corrosive, obacunone and ursolic corrosive were found to achieve success against the target proteins of SARS-CoV-2. [5] Thus, ADMET plays an important role within the drug discovery process.

2. OVERVIEWS OF CURRENT APPROACHES UTILIZED IN CADD

The enhancement in computational power and technology during the past 30 years have allowed an excellent help in drug discovery.

Several drugs like imatinib and zanamivir and nelfinavir are discovered with the help of molecular techniques.[6]

Some of the concepts are big data, homology modelling, virtual screening, molecular docking, De novo design, fragment-based screening, QSAR, molecular similarity, etc. [6]

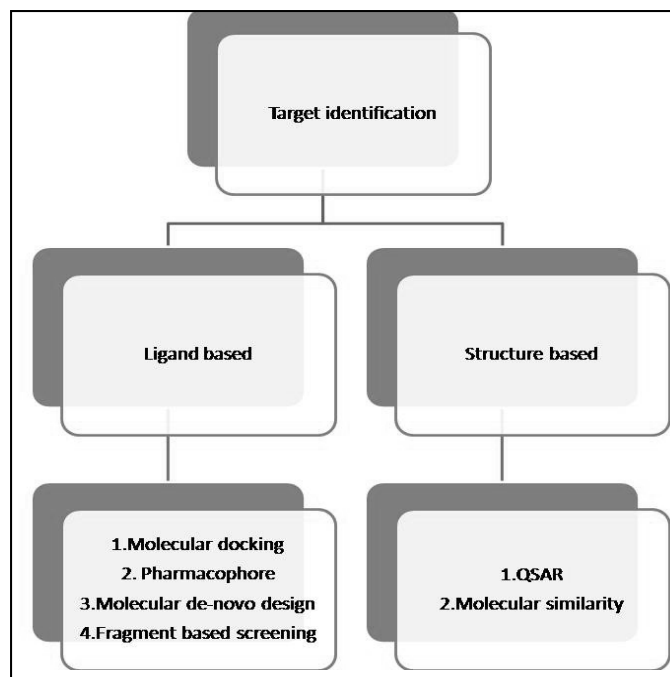Fig. 1 shows the Schematic overview of a representative computer-aided drug design process.

Figure 1 Schematic overview of CADD process
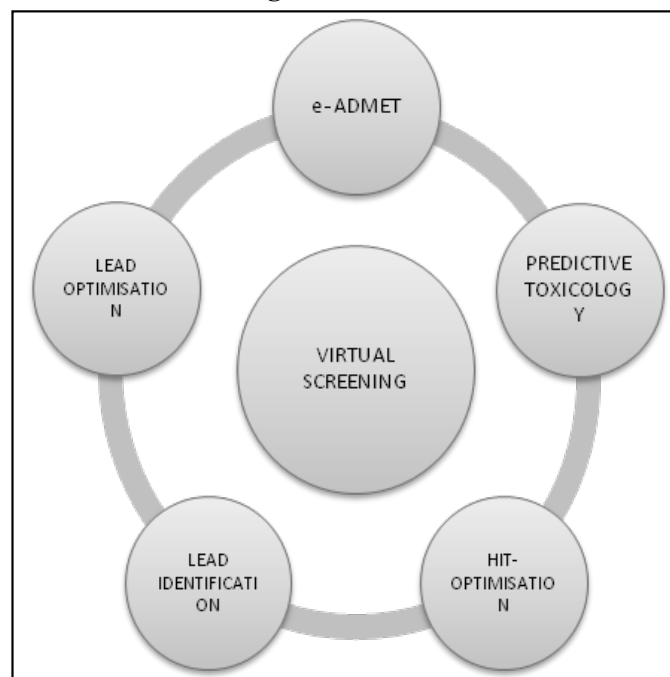
2.1 Virtual Screening

Figure 2 Virtual Screening

It is a very convenient tool nowadays for locating out the most favourable biologically active compounds with the assistance of data about the target protein.

They are of two types i.e., Structure based virtual screening approach and ligand based virtual screening approach.

SBVS depends upon the structure of target protein site and LBVS depends on the known active ligands. [7]

2.2 Ligand Based Virtual Screening

An approach to LBVS is to use 2D chemical similarity analysis methods, with this, we can scan a database of molecules against one or more active ligand-based structure. [8]

Also, similar shapes of known molecules in order that the molecules will fit into the target site can be searched and identified. [8]

2.3 Structure Based Drug Design

It involves the docking of ligand candidates into a protein target. [8]

2.4 Molecular Docking

Molecular docking is an in-silico method which is useful find the location of ligands within the site of the receptor. It has mainly 3 goals i.e., Prediction of binding pose, bio affinity and virtual screening. [7]

3. APPROACHES TO MOLECULAR DOCKING-

3.1 Simulation Approach

In this type, the target and ligand are separated by physical distance then the ligand is allowed to bind into the groove of target in its conformational space. They interact by means of H-bonding mostly. [9]

3.2 Shape Complementarity Approach

During this approach, ligand and target are employed as surface structure feature that gives their molecular interaction. [9]

3.3 Types of docking

(a) **Rigid docking (lock and key**) – the interior geometry of both the receptors and ligand are rigid. [10]

(b) **Flexible docking (induced fit)** - During this, the rotation of one of the molecules is performed. [10]

Docking algorithms-

(a) **Search algorithm-**All the possible optimal conformations for a given complex are determined and the energy of the interactions which of the resulting complexes is calculated. [11]

(b) **Scoring functions-** The binding affinity between two molecules, and also the strength of intermolecular interaction between protein & protein, protein & drug, protein & DNA is determined [11].

Docking programs

DOCK

- Auto Dock
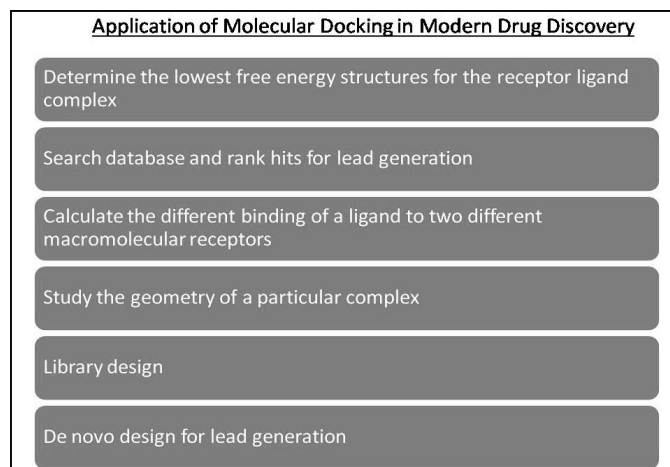- Rosetta Dock
- GOLD
- SANJEEVNI
- GRAMM
- Gem Dock

Figure 3 Applications of molecular docking

4 BIG DATA

The interaction of massive data and AI is so useful in drug discovery and development. [6] They help to lower the value and timing of drug trials, through this, it's possible to gather, check and analyse molecules in a systematic and logical manner. [12]. Shows the importance of massive data analysis within the pharmaceutical field.
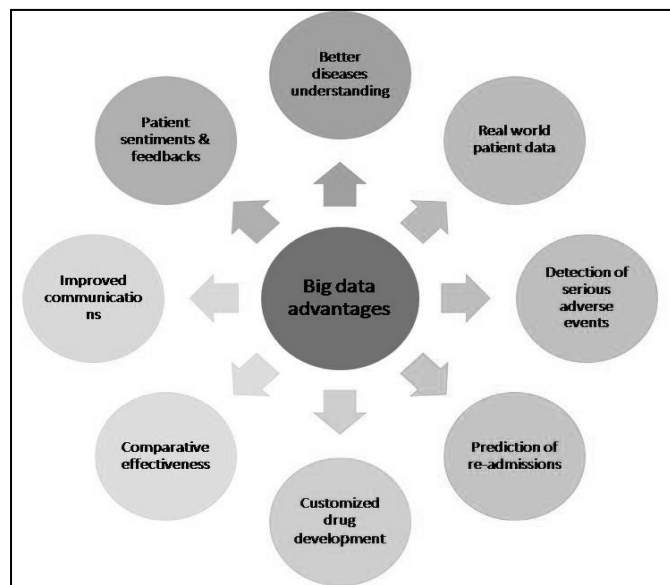

Figure 4 Usefulness of big data in Pharma and R&D

4.2 Applications of Big Data In CADD

(a) To increase the probability of a drug molecule and making it undergo clinical trials.

(b) In gene & genomics for the interpretation & validation of biological data.

(c) Processing, integration and interpretation of huge biological datasets are enabled by applications of machine learning & artificial learning.

(d) Facilitates the access to large resources [13,14]

5 HOMOLOGY MODELLING

When experimental structure isn't working, computational methods are often used to predict the 3D structure of target protein. [1] It's a sort of comparative modelling during which involves-

Identification of related proteins for template structure.

(a) Proper alignment of target or template protein.

(b) Copying coordinators for confidently aligned regions.

(c) Constructing missing atom coordinates of target structure.

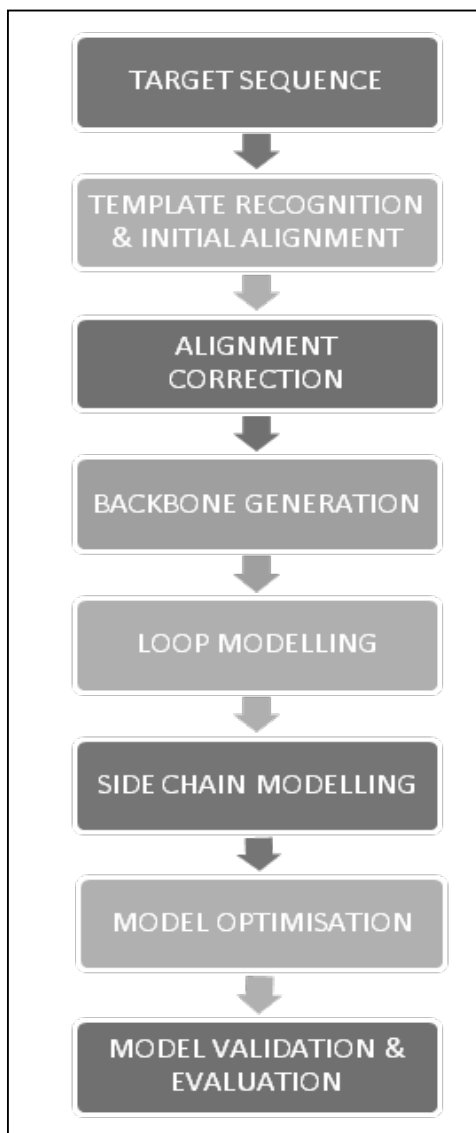(d) Model refinement and evolution.

Figure. 5 Homology modelling

The assumption within the homology modelling approach is that proteins with similar aminoalkanoic acid sequences share similar structures. It maps the aminoalkanoic acid sequence from the protein we might predict onto the experimental structure of template. The identification of candidate templates is done by sequence alignment. [15]

6. OTHER APPROACHES TO PROTEIN STRUCTURE PREDICTION

6.1 Threading (Fold Recognition)

This method differs from homology modelling such that it identifies sequences with similar protein folds that exhibit less sequence similarity. Candidate templates are identified by profile alignment methods, then, the query sequence is mapped onto the template scaffold. [16]

6.2 Abs- initio protein modelling-

It works to create proteins from scratch, instead of solved structures. It depends on biophysical protein principles & immense computational resources to make protein models. [16]

6.3 De Novo Design

De novo drug design may be a CADD technique which is sort of a puzzle where atoms or small fragments are fitted into the 3D structure of a binding site.

After that they're connected by linkers. [6]

6.4 Fragment Based Screening

FBS (Fragment based screening) is employed within the discovery of lead molecules in fragment-based lead discovery.

It is a very popular method for screening molecules with a greater success rate in generating chemical series with lead like characteristics. Fragment protein interactions are detected by higher sensitive NMR spectroscopy [17].

Table 1 : Difference Between Fragment Based Screening [17-22] & De-Novo Design [23]

FRAGMENT BASED SCREENING	DE- NOVO DESIGN
• It is the method for the discovery of lead molecules. • It is the process for the detection of very small molecules or "fragments" binding to the specific target. • It helps to design multitarget drugs for multiple diseases. • This type of drug design open up new polypharmacological avenues for discovery of innovative and effective therapies.	• It is the process in which the 3D structure of receptor is used to design newer drug molecules. • It involves structure determination of lead target complexes. • It helps to design the lead modifications using molecular modelling tools. • It can help to deisgn new class of chemical compounds

7. QSAR

Quantitative structure activity relationship gives information regarding the relationship between the chemical structure and biological activity within a mathematical model i.e.

Activity = f (physiochemical properties and/or structural properties) + error

The error includes model error (bias) and observational variability, that is, the variability in observations even on an accurate model. [24] The main use is to spot the properties of novel compound where synthesis and testing isn't required. QSAR modelling has been used as a lead optimization approach in drug discovery and research. However, in recent years QSAR modelling has found broader applications in hit and lead discovery by the means

of virtual screening also within the area of drug-like property prediction, and chemical risk assessment. [25]

7.1 Types of QSAR

7.1.1 1D-QSAR fundamental molecular properties are correlated viz. pKa, log P with biological activity.

7.1.2 2D-QSAR- varied 2D properties are correlated i.e., physio-chemical properties with biological activity.

7.1.3 3D-QSAR-varied 3D properties surrounding the molecule are correlated, e.g.; COMFA, COMSIA, MFA, GRID etc.

7.1.4 4D-QSAR- the ligand receptor interaction of the drug molecule with the 3D properties are introduced.

7.1.5 5D-QSAR- explicitly represent different induced-fit models in 4D-QSAR

7.1.6 6D-QSAR- further incorporating different salvation models in 5D-QSAR. [26]
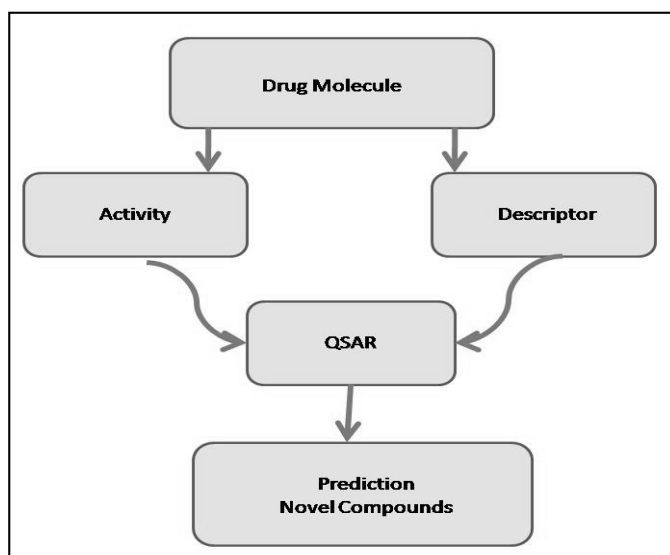

Figure 6 QSAR module

8. MOLECULAR SIMILARITIES

Molecular similarity refers to the similarity in the chemical elements, molecules or chemical compounds with reference to either structural or functional qualities. [27]

The idea of molecular similarity is employed in chemo informatics. It plays a crucial role to predict the properties of chemical compounds, designing chemicals and conducting drug design studies by screening large databases containing structures of chemicals.[27]

Molecular similarity is simpler than QSAR. According to it; similar compounds will have similar activity. So, it's will not filter the compounds from pre-existing databases.

9. PHARMACOPHORE MODELLING

Pharmacophore is defined as 3D arrangement of chemical functional groups, which show biological activity.

It tells us about the molecular interactions of various compounds to their target structure, complimentary to their 3D space.

It is generated with the assistance of- one active molecule, a series of active molecule, site of target protein and protein-ligand complex.
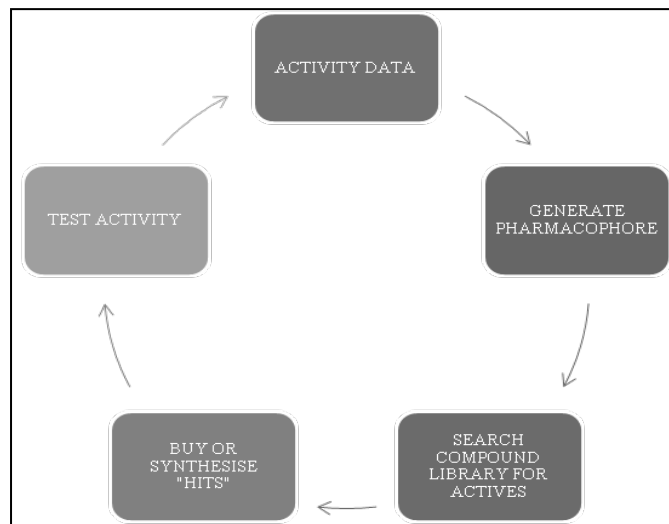

Figure 7 Pharmacophore modelling

Depending on the sort of the experiment, different strategies are available, which are either in ligand-based manner or in structure-based manner.

9.1 Structure Based Pharmacophore Modelling

Chemical features of the site and sterical relationships from 3D structure of macromolecular target or macromolecule- ligand complex is generated. It shows the possible interaction sites between macromolecular target and ligands [28]

9.2 Ligand Based Pharmacophore Modelling

It's an important strategy within the absence of macromolecular target structure. In it, the common chemical characteristics from 3D structure of multiple known ligands are extracted through a ligand alignment, which represents the interactions between ligands and potential macromolecular target [28]

9.3 Classification

There are mainly 4 types of approaches computer aided drug design are the following:

(a) Structure based drug design/direct approach

(b) Ligand based drug design

(c) Hybrid methods.

(d0 Fragment based drug design

9.3.1 Structure based drug design

In SBDD structure of the target protein is known and the calculation of bio affinity takes place after the method of docking to style the new drug molecule.
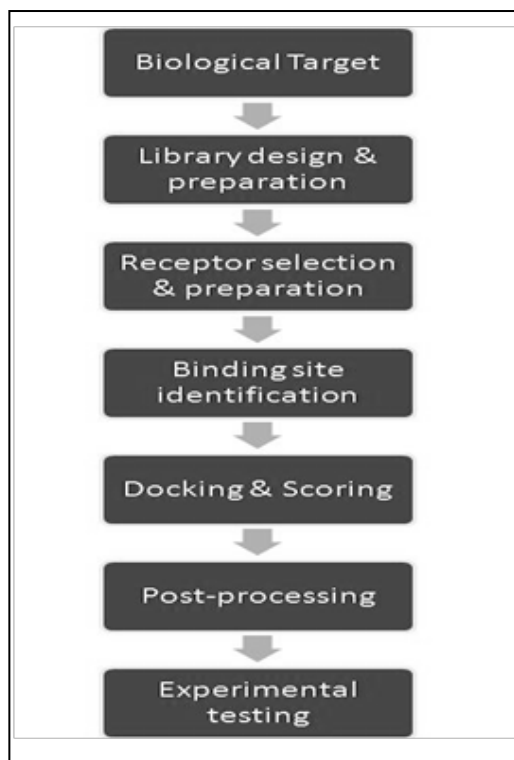
Figure 8 Structure based drug design

It involves various cycles before clinical trials i.e. First cycle comprises of isolation, purification and structure determination of the target protein. The second cycle comprises of structure determination of the protein in complex with the optimistic lead of the primary cycle. Structure-based methods depend upon the 3D information of the molecular target. Examples are docking and molecular dynamics (MD). Applications of structure-based methods include characterization of binding sites, elucidation of the mechanism of action of active molecules at the molecular level, and assessment of the kinetics and thermodynamics involved in ligand-target recognition. [29]

9.3.2 Ligand based drug design

The LBDD approach involves the analysis of ligands which are to be bounded to the target of interest. The most important objective is to retain the essential physicochemical within the compounds. It is called as indirect approach also because it doesn't involve the knowledge of the structure of the target of interest. Ligand-based methods are supported the knowledge of the chemical structures of a group of ligands with known biological activity. Bioactive compounds are spotted using this technique or the activity of active molecules is improved. Typical samples of ligand-based methods are similarity searching and QSAR modelling. [29]

9.3.3 Hybrid methods

When the structure of target and that of active molecules is understood, we use hybrid or combined methods which are basically a mixture of structure based and ligand-based methods. Examples are pharmacophore modelling, in silico approaches, etc.

9.3.4 Fragment Based Drug Design

Also referred to as fragment-based lead discovery, it's a way which is used for locating lead compounds as a neighbourhood of drug discovery process. Within the fragment-based approaches, low relative molecular mass chemical fragments are initially selected and their ability to bind to the target is tested. These fragments are the building blocks of the complex lead series. [30]

10. WORKING OF CADD

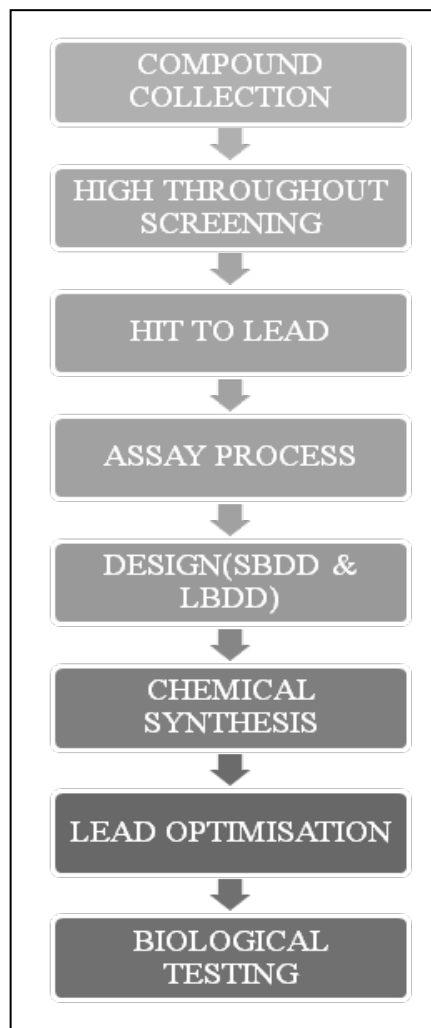FIG shows the workflow of the drug discovery process.

Figure 9 Drug Discovery Cycle

The major steps involved within the process are-

(a) TARGET IDENTIFICATION – genetics, biology, bioinformatics

(b) STRUCTURE DETERMINATION- X-RAY crystallography, NMR spectroscopy

(c) BIOLOGICAL ASSAYS- Molecular modelling, special effects

(d) SYNTHETIC CHEMISTRY- peptidomimetics, combinatorial chemistry

(e) CLINICAL TRIALS

11 MAIN APPLICATIONS OF CADD

CADD methods are used for:

- Analysis of target structure.
- Generation of candidate molecule.
- Docking of generated molecules with target
- Having a hint of bio affinities of drug.
- Optimisation of molecules for further improvement.
- Filtration of huge compound library into small sets.
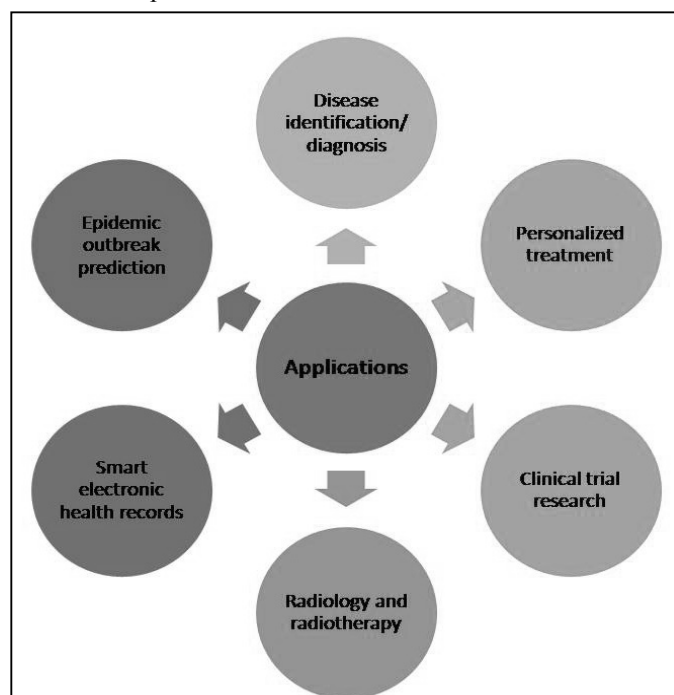- Hit finding.
- Lead optimisation

Figure 9 Major applications of CADD

12. APPLICATIONS OF MACHINE LEARNING IN CADD

Drug discovery and development depend upon numerous factors, machine learning is one among them. Machine learning approach provide a group of tools which will improve the drug discovery and deciding with a top-quality data. Examples- target validation, identification of prognostic biomarkers and analysis of digital pathology data in clinical trials. [31, 32]

Major applications include:

- Disease identification/ diagnosis
- Personalized treatment/behavioural modification
- Drug discovery/manufacturing
- Clinical trial research
- Radiology and radiotherapy
- Smart electronic health records
- Epidemic outbreak prediction

13. MOLECULAR DYNAMICS

Molecular dynamics (MD) may be a simulation method which is used to analyse the physical movements of atoms and molecules. The atoms and molecules are allowed to interact for a hard and fast period of time, giving a view of the dynamic "evolution" of the system. [33] Molecular dynamics has evolved since 1970s. Its major limitation is scalability which is due to large calculations for several particles, thus it needs a high CPU capability to handle an outsized number of calculations. Another issue is latency because the processors must be in constant communication, an efficient infrastructure is required otherwise may end in slow computing. The solution for this issue is often GPU (graphical processing units). Now here is a general outlook to the main aspects and theories behind MD.

14. GENERAL ASPECTS

It involves the applications of the laws of motion to the molecules. For this, firstly a molecule is mentioned a group of spheres where the bonds are springs.

Then parameterization takes place i.e., certain values are assigned and experimental and theoretical information is provided. The parameter sets consist of charges, bonding and non-bonding interactions, polarisations, torsions etc. [33]

15. APPLICATIONS OF MOLECULAR DYNAMICS IN CADD

It has been referred to as the successor to molecular docking. It's mainly utilized in putative allosteric sites and binding mode studies. It is used to refine the 3D structure of protein and other macromolecules with the help of X-RAY crystallography and NMR spectroscopy. The physical properties of Nano technological devices are identified, also, to review the motion of macromolecules. [33]

16. QUANTAM MECHANICS – APPLICATIONS IN CADD

(a) QSAR model combined with quantum physics helps with the prediction of the drug ADMET & gives information on how the modification of a compound affects the pharmacokinetic profile of the drug. [34]

(b) This approach provides accuracy in structure-based separation energy.

(c) They are incorporated into docking procedures.

(d0 It is useful in providing information about QSAR & 3D conformation of ligands. [34, 35]

17. DENSITY FUNCTIONAL THEORY IN CADD-

Density functional theory is known to be a computational quantum mechanical modelling method utilized in physics, chemistry & material science to research and identifying the electronic structure. The property of electron systems is often determined by using functional. In DFT, we consider density functional in situ of wave functional. [35]

DFT: add terms of density

E = E [n(r)]

Ψ2 = n(r)

DFT may be a quantum mechanical method which is employed to unravel pharmaceutical problems. It's also helpful to describe biologically relevant molecular systems at an inexpensive cost. [36]

18. ADVANTAGES OF CADD

The major advantages of CADD are:

- Reduction in biological testing efforts.
- Cost effective.
- Time saving.
- Minimize the prospect of failures,
- Gives a thought of drug receptor interaction pattern.
- Designing of novel drugs having various functional groups during a single compound.
- Allows Comprehensive and detailed study of the compounds of interest. [37]

19. CHALLENGES AND EMERGING PROBLEMS IN CADD

The biggest challenge within the drug discovery is to contemplate target flexibility. Toxicity prediction model helps in finding out the toxicity of drug candidate to liver, kidney, heart, lung and other organs. To come up with a pharmacological effect, a candidate drug must reach to specialise in by passing various physiological barriers, just like the gastrointestinal barrier, the blood–brain barrier and also the microcirculatory barrier. Lack of reliable experimental data and parameters related to ADME and toxicity limits the accuracy of prediction models. Only 40% of drug candidates in trial get approval for large scale synthesis and marketing. There is also a risk that a possible, safe and biologically active drug candidate has not been considered by predictive computational model. Accuracy of these predictive models is usually improved by adding more reliable data and important parameter related to toxicity.

There is a desire to style a high-quality database for drug designing that need to contain information about mechanism of a specific disease, genomic and proteomic data, potential drug targets, natural leads, physicochemical properties, Pharmacophore, QSAR and ADMET models, previous efforts made in drug discovery, success/failure, run data, efficacy and side effects. [38] Drug designing is an art; the appliance of computer will help to make it more rational and successful within the longer term. Extensive use of computational approaches with higher accuracy could reduce the overall cost and failure of drug designing. Thus, the emerging problems should be checked and improved so on create the long run of drug discovery a brighter one. [37, 38]

20. CONCLUSION AND FUTURE ASPECTS

Computer aided drug design is a very important and price effective method within the field of drug discovery and development, and consistent with the past developments during this field. It's clear that it's playing a really important role in the upcoming future. It's a wonderful area for the researchers from information technology, medicine, pharmacology etc. to get new tools or to reinforce the already discovered tools to assist the drug discovery process. These techniques are very affective and thus promising a bright future within the field of drug discovery and development. Plus, it also provides us with the knowledge within the field of AI, big data, docking, molecular mechanics or dynamics, etc. Thus, this is often the longer term of our drug discovery and development.

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