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A Review On CADD: Recent Advancement In Drug Development And Applications.

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ABSTRACT

In today's world, which is full of technological advancement and scientific approaches, computers play a crucial role in every segment, including healthcare and pharmaceuticals. Computers have emerged as a boon for pharmaceutical researchers and manufacturers, as they have enabled them to discover and develop new drug components in less time, at a lower cost, and more precisely. Various elements of computer-aided drug development, which include molecular docking, quantitative structure-reactivity relationships (QSAR), virtual screening, homology modeling, and three-dimensional (3D) pharmacophore mapping, In summary, computers have become a key component for healthcare providers and pharmacy professionals as they have various applications such as computer-aided drug design, surveying, pharmaceutical analysis, pharmacovigilance, diagnostic laboratories, toxicology, risk management, etc.
Keywords: computer-aided drug design, drug design, and virtual screening.

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INTRODUCTION

Computer-aided drug design is a computational approach that is used to do the analysis, discovery, and development of the drug and its active molecules with similar biological and chemical properties. In 1981, computer-aided drug design (CADD) played a vital role in the establishment of modern trends for chemical identification and modification in the drug discovery process. Compared to High-Throughput Screening (HTS), it is an advanced process as it involves little prior information regarding the chemical structure and its design, but it can produce several hit compounds from which interesting candidates have been chosen. CADD's main function in drug discovery is to separate a large number of compound libraries into a smaller amount of predicted active compounds, allowing lead compounds to be optimized by improving biological properties and synthesized from a nucleating site by combining fragments of optimized function. [1]

Objectives of CADD

- Random screening against illness assays
- Targeted screening against disease assays
- Synthetic chemicals vs. natural products
- Rational medicine development and testing
- Increase the speed of the screening process
- Increase the efficiency of the screening
- Design from scratch
- Testing as part of the design process
- Quick failure of medications.

Advantages

- Cost savings.
- Less time to market, as CADD's anticipating power, aids in the identification of expected lead candidates, minimizing time spent on dead ends.
- Assists scientists in reducing the amount of time and money spent on synthetic and biological testing by focusing solely on the most promising substances.
- Simplify and speed up the difficult task.
- Increases the accuracy of results by double-checking computations.

Disadvantages

- Targeted systems are cleared quickly.
- Immune reactivity to carrier systems is given i.v.
- Inadequate targeting of targeted systems within tumor cells.
- Drug release, diffusion, and redistribution.
- Formulation necessitates exceedingly advanced technologies.
- Manufacturing, storage, and management skills are necessary.
- The toxic effect may arise due to drug decomposition at the target site.
- It's difficult to retain the dosage form in a stable form.

Constituents of CADD

CADD has five constituents namely Molecular docking, Quantitative structure reactivity relationship (QSAR), Virtual screening, Three-dimensional (3D) pharmacophore mapping, and Homology modeling as described in figure 1.

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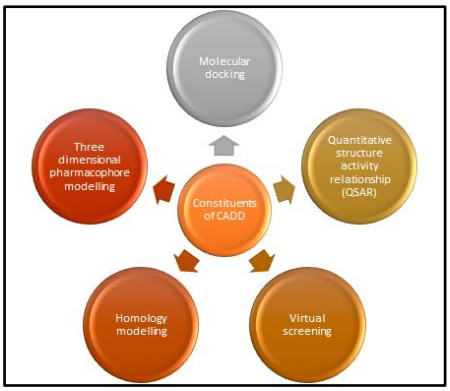

Figure 1: Main Constituents of CADD

Molecular docking

It is a method of gathering information about small molecules at the target protein's binding site by using an atomic-level model of the interaction between a small molecule and a protein. [2] The process of molecular docking can be explained in figure 2.

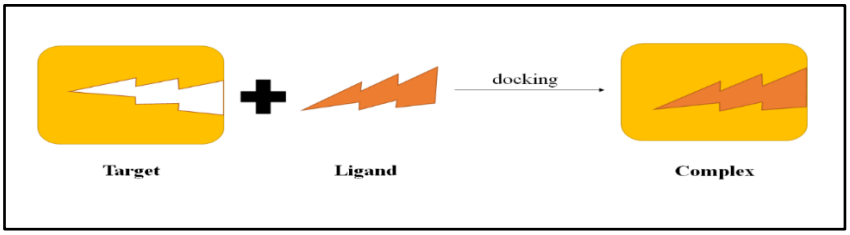

Figure 2: Molecular docking [3]

Quantitative structure reactivity relationship (QSAR)

It is a regression or classification type of model that is being employed in biological and chemical sciences and engineering. In this type of modeling, the prediction will consist of the physical and chemical behavior of the chemicals used. [4]

Virtual screening

Virtual screening is a computer-based method used to search references of small molecules to identify their structure, which prominently attaches to the drug target in the drug discovery process.

Three-dimensional (3D) pharmacophore mapping

A major weapon in trial and hit identification, optimization of the leads obtained, and designing novel drugs is a sub-part of computer-aided drug design called pharmacophore mapping.

This can be used to picture and analyze molecules on a 2D or 3D level by highlighting the key points of molecular recognition. [5]

Homology modeling

It may be defined as a modeling technique where the prototype design and the proteins at the target site may have the same routes of evolution. There are various programs and servers in existence that functionalizes the procedure of homology modeling such as PSIPRED and MODELLER. It works on the principle of protein-ligand complex formation, where the proteins act as the binding moiety. [6]

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Importance of CADD in drug discovery and development

CADD plays a key role in drug discovery and development and the phenomenon of drug discovery can be explained with the help of the drug discovery cycle as shown in figure 3.

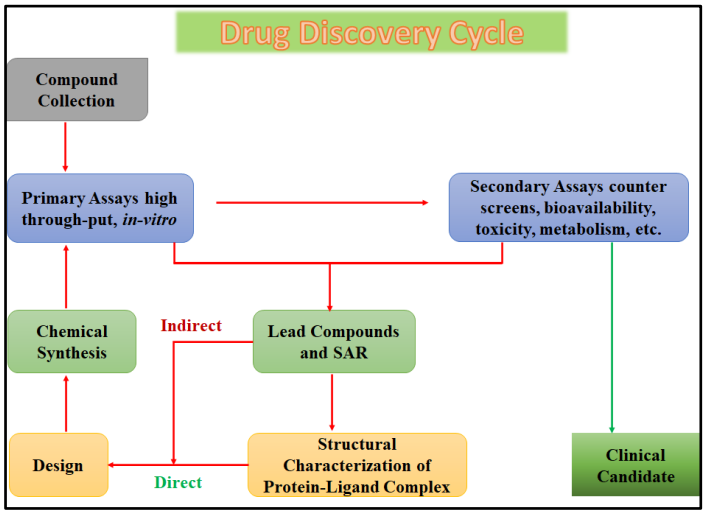

Figure 3: Drug Discovery cycle [3]

- A large number of compounds from libraries can be filtered into smaller sets of compounds that show significant activity; these compounds are then tested experimentally.
- It also gives us knowledge regarding the optimization of lead compounds and informs us about the pharmacokinetic properties like ADME (absorption, distribution, metabolism, excretion), bio-affinity, and toxicological effects.
- It helps us design new chemical compounds containing one functional group or new chemical compounds formed by joining different types of fragments. [7]

Table 1: Shows the list of some marketed pharmaceuticals whose discovery is assisted by computer.

Drug discovery assisted by computer of some of the marketed pharmaceuticals				
Generic name	**Brand Name**	**Year approved in the United States**	**Discovery assisted by**	**Activity**
Losartan	Cozaar	1994	CADD	Anti-hypertensive
Ritonavir	Norvir	1996	CADD	Antiviral
Indinavir	Crixivan	1996	CADD	Antiviral
Zolmitriptan	Zomig	1997	CADD	Antimigraine
Dorzolamide	Truspot	1995	CADD/SBDD	Antiglaucoma
Norfloxacin	Noroxin	1983	QSAR	Antibacterial
Lopinavir	Aluviran	2000	SBDD	Antineoplastic
Imatinib	Gleevec	2001	SBDD	Antineoplastic
Erlotinib	Tarceva	2004	SBDD	Anticoagulant

CADD: Computer Assisted Drug Design, QSAR: Quantitative structure-activity relationship, SBDD: Structure-Based Drug Design [8]

Drug design

Drug design is the process of developing a new chemical entity that is chemically and biologically active based on the study of various receptors at the target site.

Drug design is of basically two types Ligand-based drug design and Structure-based drug design as shown in figure 4.

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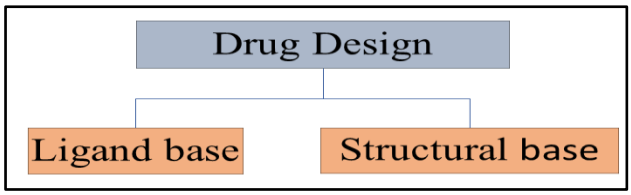

Figure 4: Types of Drug Design

Computer-aided drug design based on Ligand

- Drug development based on ligands' Potency and other critical qualities is enhanced by building suitable analogs based on knowledge of the structure-activity relationship (SAR).
- Ligand-based drug development starts with either a single chemical or a series of compounds known to be potent against a target.
- Computational techniques such as pharmacophore modeling and compound shapes are very advantageous for design objectives. Once a large dataset with a wide variety of potencies is available, a Quantitative Structure-Activity Relationships (QSAR) model can be tried and used if the models are strong enough for prediction. Machine-learning-based models can also be used if the target is well-known and has a large number of compounds already identified in public literature or databases.

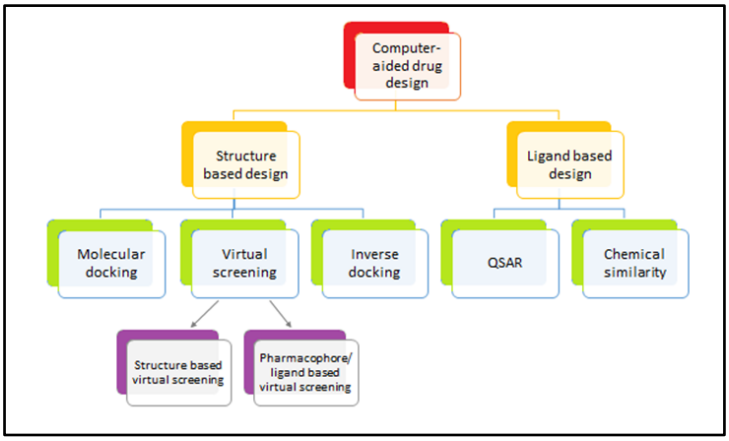

Figure 5: Computer-aided drug design based on Ligand

Computer-aided drug design based on the structure

Based on knowledge of the biological target's three-dimensional structure, this can be achieved by:

- X-ray crystallography is one type of x-ray crystallography.
- Spectroscopy using Nuclear Magnetic Resonance (NMR): NMR spectroscopy is a technique for determining the chemical composition of a substance, while X-ray crystallography is a technique for determining the structure of a substance. Drug development based on structure, if a target's experimental structure is not available, homology modeling of the target based on the experimental structure of a comparable protein might be considered. Building an atomic-resolution model of the "target" and an experimental three-dimensional structure of a comparable homologous protein is referred to as homology modeling, also known as comparative modeling of proteins. [10,11]

Methods of drug design based on the structure

Virtual Screening

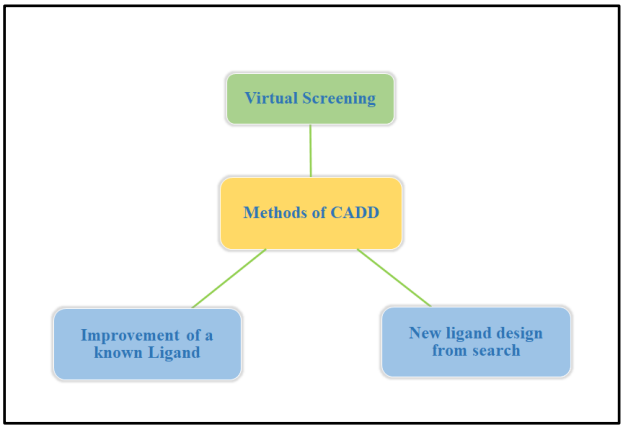

Figure 6: Virtual Screening

- Virtual screening (VS) is a quantitative technique used in drug development to search libraries of small compounds for structures that will perfectly bind to a therapeutic target, which may be a protein receptor or any enzyme. [12]
- The term "virtual screening" refers to the process of "automatically analyzing very vast libraries of chemicals" with the help of computer algorithms. As this characterization implies, VS has essentially been a numbers game, to narrow down the vast chemical space of over 1060 possible molecules to an achievable number that can be acquired, synthesized, and tested. [13]

Virtual screening based on structure (SBVS)

Structure-based virtual screening, one of the most optimistic in silico methods used for drug research, is flexible and useful in these conditions. Structure-based virtual design uses scoring functions to assess the force of non-covalent contact between a ligand and a molecular target, and it tries to forecast the optimum interaction mode between two compounds to design a stable complex. [14]

Significance of SBVS in the drug development process:

- Protein Preparation Schemes for SBVS
- Preparation of a compound database
- Library Design
- Docking and Scoring

Ligand-based virtual screening

An effective similarity measure and a reliable scoring system are the two important elements of a ligand-based quantitative technique. Furthermore, the computational technique should have the ability to screen a large number of candidate ligands accurately.

Ligand-based virtual screening methods identify and optimize leads based on the information found in known active ligands rather than the structure of a target protein. A scoring technique for ligand-based screening should effectively distinguish between active and inactive compounds and be able to quickly select a small number of active compounds from a library that contains a high number of inert compounds. [15,16,]

Limitations of CADD

Despite the emergence of the several pioneering methodologies outlined above, drug design and development remain an inherently risky enterprise with high input costs and a poor success rate. In

general, just one out of every 1000 lead compounds make it to phase 1 clinical trial, and only one out of every five pharmaceuticals make it to the market from phase 1 studies. Some computer-aided drug design techniques take a long time, especially when seeking the right lead component.

Application of computers in the field of pharmacy and healthcare:

A computer is widely used in the field of pharmacy as it can perform arithmetic and logical operations. According to the requirement, and software installed. The uses of computers in pharmacy and healthcare are as follows: [17] Figure 7.

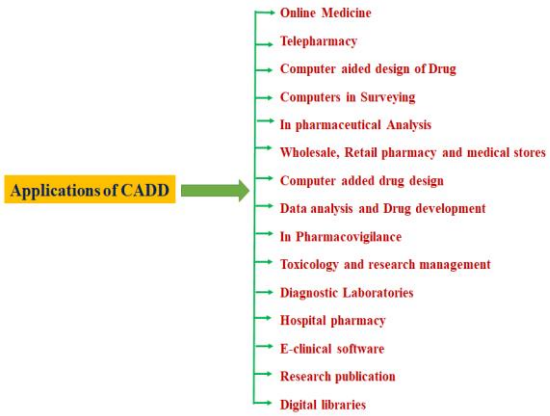

Figure 7: Applications of CADD

Online drug pharmacy

Online shopping is very popular and very convenient, as anyone can order medicine in a very short period by just uploading the prescription medicine and the medicine is delivered to the doorstep. [18] There are a large number of applications available which are popular among all to order medicine such as-

- NetMeds
- Pharm Easy
- Easy Medico
- Buy Drug
- Apollo Pharmacy, etc.

Tele-pharmacy

It is the modern method of interaction between the doctor and patient by various methods using the internet: via video call, email, voice mail, video conferencing, social media platforms, etc.

In this case, the doctor examines the patient's health condition and prescribes medication and consultations accordingly; and can also refer him to another expert.

Computer-aided design of Drug (CADD)

It is an advanced method of designing drugs. It uses graphic software, which helps to design a new molecule and improves the efficacy of previously known products. [18]

Use of computers in surveys

Computers are widely used for surveys due to the ease of data handling, data collection, maintaining records, evaluation of data, and prediction of future aspects concerning the same. It can be employed in the handling of data for drug development from its grassroots to its clinical trials and helps

to analyze the data associated with it, such as the data related to its pharmacokinetics, pharmacodynamics, toxicity, ADRs, pharmacological effect, etc. [19]

Application in Pharmaceutical Analysis

Various instruments used in pharmaceutical analysis, like UV-visible spectrophotometers, infrared instruments, HPLC, mass spectrometers, microscopes, NMR, etc. utilize computers and various software for data processing, data storage, and analysis of the compounds.

It helps us to analyze the compound and evaluation of the data obtained in less time and convenient manner. [8]

Wholesale, retail pharmacy, and medical stores

Computers are used by the pharmacist in the medical store to maintain records of the available stock, sold stock, preparation of bills and medical claims, analysis the sales, and sales forecasting. Various software like MS Excel, are useful in maintaining numerical records. It also helps to look out for the ordered stock and track the shipment. [18]

Computer-added drug design

Drug design can be termed as the discovery process of new medication based on the target at the cellular level. Various computer software is being employed for assistance in designing drug moiety. A variety of software is being employed, which is as follows; AutoDock, CombiBUILD, DockVision, LIGPLOT, SITUS, DOCK, etc. This software produces a molecule that acts as a lead molecule onto which the whole study is focused and produces the result of interest. With the help of the software, the time required in the development of drugs through conventional methods is reduced, and the overall cost of development of a product over time is reduced. [8]

Data analysis and drug development

Scientists and researchers from various streams will take part in the development of pharmaceuticals. The fields in which they are studying can be slightly different from one another, but later on, they will have to work with the scientific data generated. Huge amounts of applications are being filed to the regulatory authorities to get approval for conducting trials or their marketing. So, every data presented in the dossier needs to be analyzed, reported, and audited before granting approval to whatever they are seeking. The increased use of computers in the field of pharmaceutical development provided greater efficiency and productivity in product development with time. [8,20]

In pharmacovigilance

With the advancement in pharmaceutical product development, there is greater susceptibility to adverse drug reactions. So, various IT companies are assigned the task of lookup for these data and regularizing the data with time by which further risk can be eliminated. [21]

In toxicology and risk management

There were several software programs used to handle the data related to toxicology and risks associated with the drug product. [21]

- Derek Nexus
- Literature Look-up
- Metadrug
- Topkat
- Virtualtoxlab

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Diagnostic Laboratories

The manual method for diagnostics was very time-consuming and less precise. So, these are replaced by an automated, computerized instrument that gives an accurate result in less time. These instrument converts raw data into digital format and gives numerical values in reports. [22]

In hospital pharmacies

Computers are very useful in hospital pharmacies in performing different tasks such as storing details of every individual, making records of receiving and allotting drugs, records of dispensed drugs to in-patients and out-patients, information of patient records, monitoring patients' health conditions like blood pressure, pulse rate, and body temperature, patient medication history, etc. [8]

E-clinical software's

Various e-clinical software is available like Oracle clinical V4i, Data LabsXC, Cliniplus, Trial Master, etc. This software helps in the clinical research process through data collection, data entry, remote data capture, etc., and helps in the easy and quick design of experiments. [8]

In research publication

Submission and publication of research papers by researchers and scholars in handwritten form is a difficult task and it is also a tough task for the reviewers to review and examine.

Computers have made it way easier to compile, submit, and publish their research work and also reduce the chance of grammatical mistakes, plagiarism, and making the work in a common and presentable format, which also helps reviewers to analyze and publish the work in quick time.[19] The process of research publication is shown in figure 8.

Various software like Chem Draw and Corel Draw are used to draw chemical structures and 3-D models, and a Graph pad prism is used for the graphical representation of analysis data. [8]

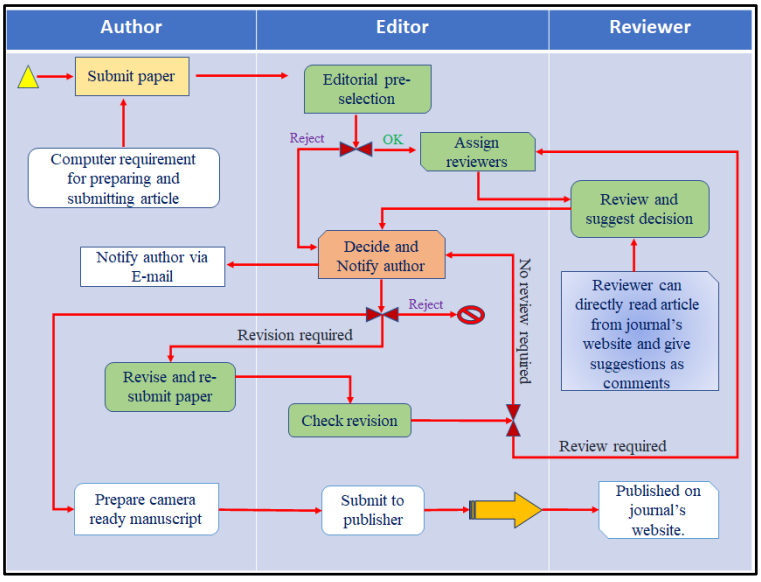

Figure 8: Process of Research Publication

Digital libraries

Digital libraries help us to access data anywhere in the world in all areas of education. Digital libraries help students, researchers, scholars, working professionals, etc. to study and enhance their knowledge of different fields without having to carry printed documents. The global expansion of the internet has increased interest in the use of digital libraries and related technologies. [8]

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