WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 17, 630-638. Review Article ISSN 2277– 7105

ROLE OF COMPUTER AIDED DRUG DESIGN IN NEW DRUG DEVELOPMENT

Jayshree Kokat[1]*, Rajesh Mokate[2], Bharat Jadhav[3] and Sharda Giram[4]

[1]Department of Pharmaceutical Chemistry, Abasaheb Kakade College of Pharmacy, Bodhegaon 414503, Ahmednagar, Maharashtra.

[2]Department of Pharmacognosy, Abasaheb Kakade College of Pharmacy, Bodhegaon 414503, Ahmednagar, Maharashtra.

[3]Department of Pharmaceutics, Abasaheb Kakade College of B Pharmacy, Bodhegaon 414503, Ahmednagar, Maharashtra.

[4]Department of Pharmacology, Abasaheb Kakade College of Pharmacy, Bodhegaon 414503 Ahmednagar, Maharashtra.

Article Received on
03 November 2022,
Revised on 24 Nov. 2022,
Accepted on 14 Dec. 2022
DOI: 10.20959/wjpr202217-26550

***Corresponding Author**
Jayshree Kokat
Department of Pharmaceutical Chemistry, Abasaheb Kakade College of Pharmacy, Bodhegaon 414503, Ahmednagar, Maharashtra.

ABSTRACT

The process of developing a new drug is typically regarded as extremely complicated and time- and resource-intensive. As a result, computer-aided drug design methods are now widely used to improve the drug discovery and development process. Between all of these structure-based drug design and ligand-based drug design approaches, which are known to be very effective and powerful techniques in drug discovery and development, various CADD approaches are evaluated as promising techniques. Together with molecular docking, these two approaches can be utilized in virtual screening for lead identification and optimization. Computational tools are now widely used in pharmaceutical industries and research fields to boost drug discovery and development pipeline efficiency. This article provides an overview of computational approaches, which are creative methods for discovering novel leads and assisting drug development research.

KEYWORDS: Computer Aided Drug Design, Molecular Docking, Pharmacophore, Drug Discovery.

INTRODUCTION

In the drug design, discovery, and development process, computational approaches are gaining rapid exploration, implementation, and admiration. Presenting another medication in a market is an extremely complicated, unsafe and exorbitant cycle with regards to time, cash and labor. The drug discovery and development process typically takes between 10 and 14 years and more than a billion dollars in capital. As a result, the computer-aided drug design (CADD) method is widely used as a novel drug design strategy to cut down on costs, time, and risk. It has been demonstrated that we can cut drug discovery and development costs by up to 50% by employing CADD strategies. The use of any software-based procedure to establish a standard for linking activity to structure is included in CADD.[1]

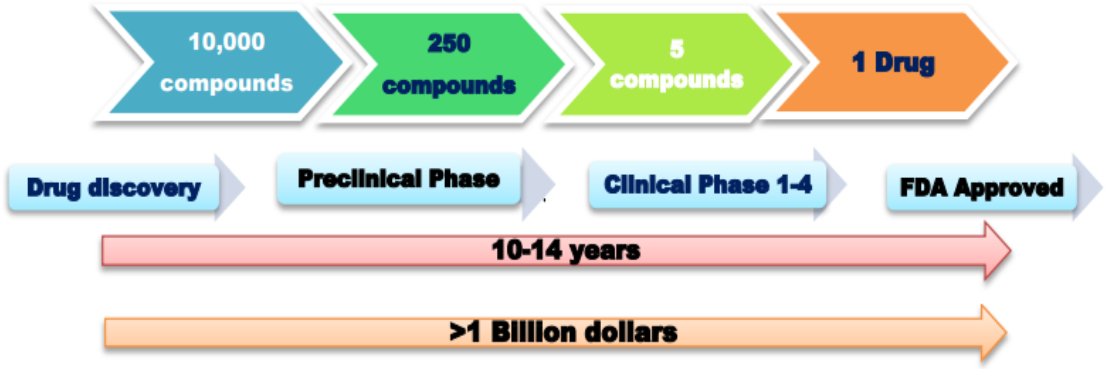

Figure 1: Traditional Method of Drug Design.

A Brief History of CADD

1900: P. Ehrich (1909) and E. Fisher (1894) proposed the receptor and lock-and-key concepts; 1970s: Limitations of the quantitative structure-activity relationship (QSAR): 2-Layered, review investigation; 1980s: X-ray crystallography, the beginning of CADD molecular biology, multi-dimensional NMR molecular modeling, and computer graphics; 1990s: Bioinformatics, combinatorial chemistry, and high-throughput screening of the human genome.

Software for Molecular Modeling

Molecular mechanics, dynamics, and multifunctional programs for general purpose molecular modeling (both of the large and small molecules); Quantum mechanics or orbital or quantum mechanical calculations for small molecules in quantum chemistry; Data set of atomic designs (enormous and little particles) — programming for stockpiling and recovery of sub-

atomic construction information; Programs for displaying molecules using QSAR (small molecules) include molecular graphics for both large and small molecules.

Software for General Purpose Molecular Modeling

For workstations, minicomputers, and supercomputers (SGI, Sun, Cray, etc.) AMBER—Peter Kollman and coworkers, UCSF. Computer assisted model building, energy minimization, molecular dynamics, and free energy perturbation calculations. Midas Plus-UCSF Computer Graphics Laboratory.[2]

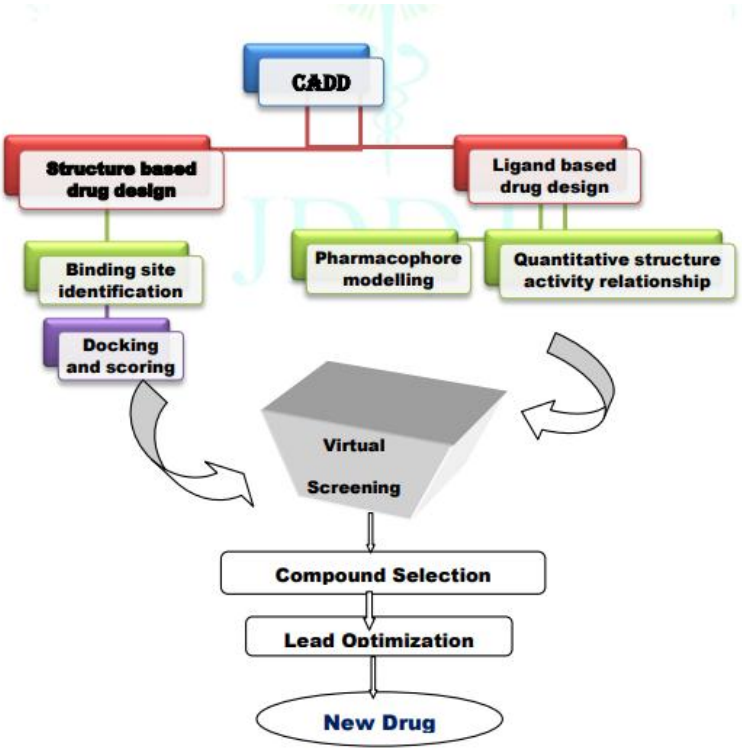

Figure 2: Computer Aided Drug Design.

Merits of CADD

1. Eliminating unwanted compounds properties like poor pharmacokinetics parameters (ADMET), poor efficacy through is sites filters
2. For experimental testing a list of compounds libraries.
3. Animals and humans models can be replaced by CADD which was traditionally used and saved both time and cost.
4. CADD also reduced the chances of drug resistance which lead to production of lead compounds that target the causative factor.
5. It also stores the high quality database and libraries for optimized use for high molecular diversity as similarity.[3]

Demerits of CADD

1. System failures may lead to the loss of all the data and designs.
2. The data and design shall always be vulnerable to viruses if not controlled with appropriate software.
3. It takes time to be technologically acknowledged / equipped.
4. Software may be costly, and upgrading it after purchase can be costly as well.
5. The operator should have proper training before operating the software.
6. System and software updates can be costly and difficult to do on a regular basis.[4]

Major types of CADD

1. Structure Based Drug Design/ direct approach
2. Ligand Based Drug Design/ indirect approach

1. Structure Based Drug Design/ direct approach (SBDD)

Based on their predicted interactions with the protein binding site, ligands are designed and evaluated in SBDD using information gleaned from a 3D macromolecule structure's binding site. As a result, the first essential steps in SBDD are locating a legitimate drug target and acquiring structural information about it. X-ray crystallography, nuclear magnetic resonance (NMR), cryo-electron microscopy (EM), homology modeling, and molecular dynamic (MD) simulations were used by structural and computational biology researchers to help create protein structures. There are two categories of SBDD. The virtual screening approach and the de novo method. The 3D receptor's information is used in de novo drug design to locate small fragments that are compatible with the binding site. To guarantee synthetic accessibility and provide a structurally novel ligand that can be synthesized for further screening, these fragments should be linked according to connection rules. Virtual screening (VS), on the other hand, makes use of small molecule libraries to find compounds that have specific bioactivity and can be used as replacements for existing ligands of target biomolecules or to find compounds for unexplored known targets with structural information that is available.[5]

1.1 Molecular Docking

The virtual simulation known as "molecular docking" is used to simulate the atomic-level interaction between a small molecule and a protein. This procedure is additionally used to describe the way of behaving of the little particles in the limiting site of target protein. The prediction of the ligand's conformation and the precise binding of the ligand within the target active site are the two fundamental steps in the docking process, which is why it is commonly

used in structure-based drug design (SBDD). This method is used to study molecular phenomena like ligand binding pose and intermolecular interaction for the stability of a complex. In the absence of knowledge of the binding site, docking efficiency is improved with complete information regarding its location. The location or active site within a protein can be identified using online programs like -GRID[19], POCKET, and others. Flexible protein docking and Flexible ligand search docking are two types of molecular docking.[6]

2. Ligand-Based drug design/ indirect approach (LBDD)

In LBDD, the ligands that bind to the desired target site are known, but the target protein's 3D structure is unknown. A pharmacophore model or molecule with all of the necessary structural features to bind to a target active site can be created using these ligands. Pharmacophore-based approaches and quantitative-structure activity relationships (QSARs) are typically ligand-based methods. Compounds with a similar structure are assumed to have the same biological action and interaction with the target protein in LBDD.[7]

2.1 Quantitative structure activity relationship (QSAR)

Quantitative design movement relationship (QSAR), a technique presented in 1960, is a helpful device to lay out quantitatively the connection between different physicochemical properties and organic action of mixtures. A singular expansion of bimolecular databases that contained information on chemical structure and, in some cases, biological activity of chemical is one of the most important goals of the new age of QSAR as an integral part of drug design and discovery.[8]

2.2 Pharmacophore

The schematic representation of bioactive functional groups along with their interatomic distance is known as ‘pharmacophore’

2.2.1 History of Pharmacophore

"Paul Ehrlich" came up with the original idea for the pharmacophore toward the end of the 1800s. At that time, it was believed that a molecule's chemical groups or functions were the cause of a biological effect, and that molecules with similar effects shared similar functions. In his book Chemo-biodynamics and drug design, Suhveler coined the term "pharmacophore," which was defined as a molecular framework carrying (phoros) the essential features responsible for a drug's pharmacon biological activity. Computer-aided drug design (CADD) relies heavily on the pharmacophore concept. Some atoms and

molecules reduce the pharmacophore, resulting in properties. These molecules can be referred to as donors or acceptors of hydrogen bonds, cations, anionic, aromatic, hydrophobic, or any combination of these terms.[6]

2.2.2 Pharmacophore Fingerprint and Model

The pharmacophore reduces the collection of molecules' 2D and 3D features. A pharmacophore unique mark addresses little particle ligand. The similarity of molecules within a library or between molecules can be examined using a pharmacophore fingerprint. Another name for the pharmacophore model is "query." In the pharmacophore model, the few features are arranged in a specific three-dimensional pattern. The pharmacophore features on screen make use of small molecules libraries.[6]

Examples

1. The influenza A virus causes the acute respiratory infectious disease known as influenza A, which poses a serious threat to human health worldwide and results in significant annual economic losses. Computer-aided drug design (CADD) offers opportunities for the rapid and effective development of innovative drugs, whereas research on traditional, innovative small-molecule drugs faces many obstacles due to the emergence of new viral strains. This provides examples of drug screening of viral target proteins using the CADD approach, as well as the viral proteins that can be used as therapeutic targets for anti-influenza drugs and play an important role in the life cycle of the influenza A virus. Last but not least, the major drawbacks of the current CADD approaches to the discovery of anti-influenza drugs as well as the future directions of the field are discussed.[9]

2. Tropical infections continue to be a major health issue in the developing world, despite the Millennium Declaration's promise of significant progress in global health in 2000. The major tropical infectious diseases of malaria, tuberculosis, trypanosomiasis, and leishmaniasis, according to recent estimates, are responsible for more than 2.2 million deaths annually and the loss of approximately 85 million disability-adjusted life years. The search for new medicines to combat tropical infectious diseases has been reenergized as a result of the critical role that chemotherapy plays in mitigating these infections' negative effects on health and the economy. At the hit identification, hit-to-lead, and lead optimization stages, computational technologies have been used more frequently in mainstream drug discovery programs as a result of the research efforts. Computer-aided drug discovery methods have been used to find new antimalarial, antitubercular, antitrypanosomal, and antileishmanial

agents, as shown in this review article. The last five years' developments are the primary focus.[10]

Target*	Function
P. falciparum macrophage migratory inhibitory factor (*Pf* MIF)[26]	*Pf*MIF is a homologue of the human immunoregulatory cytokine MIF. It is released by *P. falciparum* upon malaria infection and mediates the host's immune response. Inhibition of tautomerase activity in the *Pf*MIF may affect the cytokine activity.
P. falciparum cytochrome bc1 complex[27,62]	This is a key element in the mitochondrial respiratory chain and is essential for survival of *P. falciparum*. Blocking of the oxidation site (Qo) of cytochrome inhibits pyrimidine biosynthesis leading to parasite death.
P. falciparum FKBP35[28]	FKBP35 belongs to the immunophilin family, also known as FK506 binding proteins (FKBPs). It is involved in calcineurin pathway

Figure 3: Antimalarial drug targets that have recently been used in CADD approaches.

3. The widespread link between epigenetic dysfunction and a number of diseases, particularly cancer, emphasizes the therapeutic potential of chemical interventions in this area. With quick improvement of computational procedures and superior execution computational assets, PC supported drug configuration has arisen as a promising technique to accelerate epigenetic drug disclosure. Druggability prediction, virtual screening, homology modeling, scaffold hopping, pharmacophore modeling, molecular dynamics simulations, quantum chemistry calculation, and 3D quantitative structure activity relationship are just some of the major computational methods that have been successfully used in the design and discovery of epi-drugs and epi-probes, as reported in the literature. Last but not least, we talk about the major drawbacks of the current virtual drug design strategies for discovering drugs that target epigenetics and what the future holds for this field.[11]

4. Worldwide, serious health concerns have been raised by the recent COVID-19 pandemic, which is caused by the lethal coronavirus. It is still difficult to develop vaccines or drugs that have been approved, which further calls for the discovery of novel therapeutic molecules. By reducing costs and time, computer-aided drug design has helped to speed up the process of discovering and developing new drugs. We highlight two significant subsets of computer-aided drug design (CADD) in this overview article: as well as structured-based and ligand-based drug discovery. In structure-based drug design, molecular docking and molecular dynamic simulation are two types of molecular modeling techniques, whereas in ligand-based

drug design, pharmacophore modeling, quantitative structure-activity relationships (QSARs), and artificial intelligence (AI) are used. In the context of COVID-19, we have briefly discussed the significance of computer-aided drug design and the researchers' continued reliance on these computational methods for the rapid identification of promising drug candidate molecules against various drug targets implicated in the pathogenesis of SARS-CoV-2. Both structure-based and ligand-based drug design have been accelerated as a result of the structural elucidation of pharmacological drug targets and the discovery of preclinical drug candidate molecules. This audit article will help the clinicians and analysts to take advantage of the enormous capability of PC supported drug configuration in planning and distinguishing proof of medication particles and consequently helping in the administration of deadly illness.[12]

Drug	Year of approval	Therapeutic action
Captopril	1981	Antihypertensive
Saquinavir	1995	Human immunodeficiency Virus (HIV) inhibitor
Dorzolamide	1995	Carbonic anhydrase inhibitor
Indinavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Ritonavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Triofiban	1998	Fibrinogen antagonist
Zanamivir	1999	Neuraminidase inhibitor
Oseltamivir	1999	Active against influenza A and B viruses.
Raltegravir	2007	Human immunodeficiency Virus (HIV) inhibitor
Aliskiren	2007	Human renin inhibitor
TMI-005	Phase II clinical trials	In Rheumatoid arthritis
LY-517717	Phase II clinical trials	Serine protease Inhibitor
Boceprevir	Phase III clinical trials	Hepatitis C virus (HCV) inhibitor
Nolatrexed	Phase III clinical trials	In Liver cancer
NVP-AUY922	Phase I clinical trials	Inhibitor for HSP90

Figure 4: List of Some Clinically Approved Drug Discovered though CADD Approaches.[13]

CONCLUSON

The conventional method of drug discovery and development takes a very long time and costs a lot of money. Because of this, the CADD technique is very useful for drug discovery and development and has scope for more research in the future.

REFERENCES

1. Surabhi, B. Singh**,** Computer Aided Drug Design: An Overview. Journal of Drug Delivery & Therapeutics, 2018; 8(5): 504-509.
2. P. Kore, M. Mutha, R. Antre, R. Oswal, S. Kshirsagar, Computer-Aided Drug Design: An Innovative Tool for Modeling. Open Journal of Medicinal Chemistry, 2012; 2: 139-148.

3. V. Tomar, M. Sakharkar, In Encyclopedia of Bioinformatics And Computational Biology, 2019.
4. A. Mudgal, P. Chaudhary, A. Nautiyal, Bandana, Sahastra, S. Tangri, Review On Computer Aided Drug Desig. Indo American Journal Of Pharmaceutical Sciences, 2022; 09(5): 99-102.
5. S. Macalino, V. Gosu, S. Hong, S. Choi, Role of computer-aided drug design in modern drug discovery. Arch. Pharm. Res. DOI 10.1007/s12272-015-0640-5.
6. S. Dharampreet, K. Ramanjeet, Patil R. K, Patil H. A review on: Computer Aided Drug Design. Journal of Emerging Technologies and Innovative Research, March 2020; 7(3).
7. A. Veselovsky and A. Ivanov, Strategy of Computer-Aided Drug Design. Current Drug Targets - Infectious Disorders, 2003; 3: 33-40.
8. A. Jain, Computer aided drug design. Journal of Physics: Conf. Series, 2017; 884: 012072.
9. D. Yu , L. WanG, Y. Wang, Recent Advances in Application of Computer-Aided Drug Design in Anti-Influenza A Virus Drug Discovery. International Journal of Molecular Science, 2022; 23: 4738.
10. P. Njogua , E. Guantaib , E. Pavadaic, K. Chibale, Computer Aided Drug Discovery Approaches against the Tropical Infectious Diseases Malaria, Tuberculosis, Trypanosomiasis and Leishmaniasis. ACS Infectious Diseases, Nov 12, 2015.
11. W. Lu, R. Zhang, H. Jiang, H. Zhang, C. Luo, Computer-Aided Drug Design in Epigenetics. Front. Chem, 6: 57. 2018.00057.
12. A. Gurung, M. Ali, J. Lee, M. Farah, K. Al-Anazi, An Updated Review of Computer-Aided Drug Design and Its Application to COVID-19. Bio Med Research International, 2021, Article ID 8853056, 18.
13. N. Bisht, B. Singh, Role of Computer Aided Drug Design in Drug Development and Drug Discovery. International Journal Pharmaceutical Science and Research, 2018; 9(4): 1405-1415.