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Review article

Role of computer-aided drug design in the discovery and development of new medicinal agents a review

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ABSTRACT

Drug design and development is a time consuming and costly process. Nowadays, computer-aided drug design approaches are usually used to improve drug discovery and advancement efficiency. The role of Computer-Aided Drug Design (CADD) is a diverse discipline in which various versions of applied and basic analysis are interlinked. It is being implemented in various fields including biochemistry, molecular biology, nanotechnology etc. Various employed computational approaches includes ligand-based drug design, structure-based drug design, quantitative structure-property relationships and quantitative structure-activity. Computational techniques are commonly utilized in pharmaceutical industry and in research to improving the effectiveness of drug discovery and development. In this review, the authors have attempted to provide a broad overview of the function of CADD in modern medicine science.

Keywords: Ligand-based drug design, Structure-based drug design, Biological activity, Molecular docking, Virtual screening.

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INTRODUCTION

Medicines are necessary for the treatment and prevention of diseases. Drugs with desired properties are therefore in great demand, but the drug discovery process is time-consuming and costly [1]. This requires an interdisciplinary endeavor to develop successful and commercially viable drugs which can be achieved by the implementation of a machine or computer as it plays a significant role in almost every scientific research [2, 3]. CADD is the method that promotes the computational techniques and tools used for the development and discovery of new feasible therapeutic agents [1].

According to general estimation, it takes 10-15 years and 500-800 million USD for implementing a typical drug development process from lead identification to clinical trials. The technique of CADD is frequently utilized in pharmaceutical field to speed up the design process most efficiently [4-6]. The more recent CADD foundations have developed in the early 1970s using structural biology to alter the biological effects of insulin and direct the production of human hemoglobin [7, 8]. X-ray crystallography was a costly and slow process at that time, making it unfeasible for extensive screening in industrial labs [9]. Parallel to this, the designing of drug, and optimization are rapidly using computers for virtual screening [10]. Recent developments in DNA microarray experiments investigated thousands of genes involved in a disease that can help gain comprehensive knowledge of disease targets, metabolic pathways and drug toxicity [5].

CADD has evolved rapidly in current years, improving the understanding of multifaceted and complex biological processes and thus new pharmacologically active agents can now be established in a short period. A few examples of drugs with the year of development/approval and therapeutic activities established by CADD approaches are enlisted in Table 1. Now CADD plays a vital role in discovering new molecular moieties [4-11]. The current review emphasizes on the drug discovery procedure, primary tools, and services built to facilitate new drug candidates' search, virtual screening process from data preparation to

post-screening review, and the various applications of computer-aided drug designing (Table 1).

Table 1: List of some clinically approved drug discovered though CADD approaches

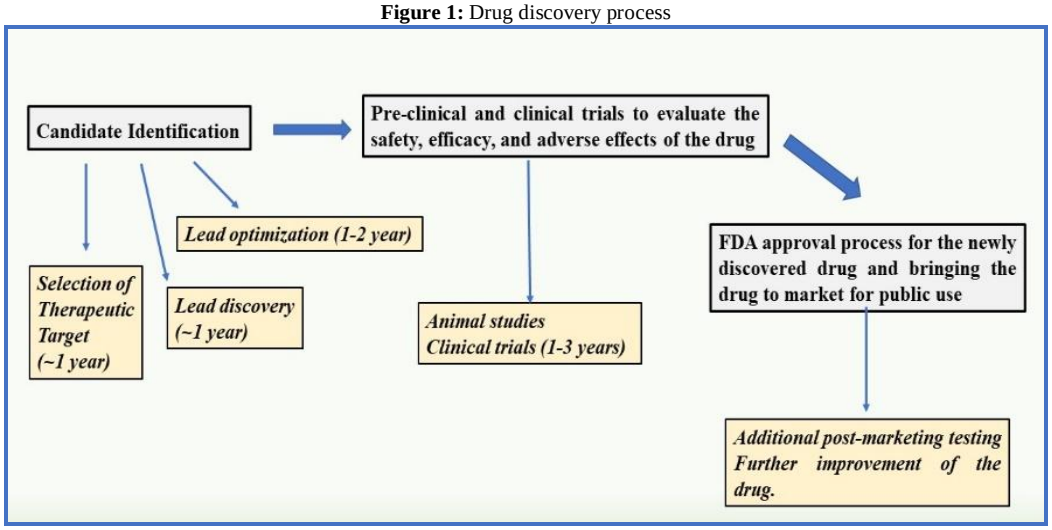
Drug	Year of approval	Therapeutic action
Captopril	1981	Antihypertensive
Zanamivir	1989	Anti- Human immunodeficiency virus (HIV)
Saquinavir	1995	HIV inhibitor
Dorzolamide	1995	Carbonic anhydrase inhibitor
Indinavir	1996	HIV inhibitor
Ritonavir	1996	
Nelfinavir	1997	Anti-HIV
Raltitrexed	1998	Anti-Cancer
Triofiban	1998	Fibrinogen antagonist
Amprenavir	1999	Anti-HIV
Zanamivir	1999	Neuraminidase inhibitor
Oseltamivir	1999	Active against influenza A and B viruses
Raltegravir	2007	Anti-HIV
Aliskiren	2007	Human renin inhibitor

DRUG DISCOVERY PROCESS

It begins with screening vast amounts of chemical compounds to refine the targets for the disease. It needs insight into the drug-receptor structure. So, the drug molecules can be tailored to the binding site. The process of drug development begins with understanding the disease for which medication is to be developed. It comprises the measures mentioned in Figures 1 and 2 [12].

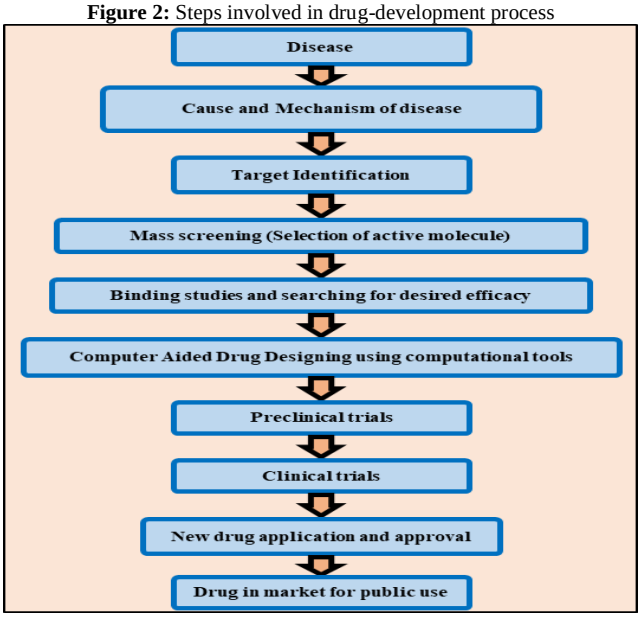
In general, new drug research and pre-clinical development are very time-consuming, and takes 3-6 years to complete. Clinical trials can take as long as 10 years or even more followed by the product launch in the market [13]. On average, around 250 compounds can clear pre-clinical trials from among the 5000-10000 screened compounds, and just 5 of them live to undergo clinical trials. In last, the FDA approves only one compound after a strenuous assessment of the newly discovered drugs [7]. Several parameters are needed to be considered while designing a drug. According to these parameters, a drug should be effective, tissue selective, safe, has good bioavailability, should be metabolically stable, and should have no or very few side effects. Some factors are there which affect the discovery and development of a drug molecule like drug development resources, an outlay of the drug development process etc [4-5].

Figure 1: Drug discovery process



CADD designs each product in a recorded manner and simplifies the production process. Computational power has enhanced CADD application in the pharmaceutical industry. Many of the approved marketed drugs have attributed their discovery from CADD tools, such as angiotensin-converting enzyme inhibitor, captopril for the treatment of hypertension [6-13] dorzolamide (a carbonic anhydrase inhibitor) for the treatment of cystoid macular edema [7-8] aliskiren renin inhibitor utilized for the management of critical hypertension [9-14].

Figure 2: Steps involved in drug-development process



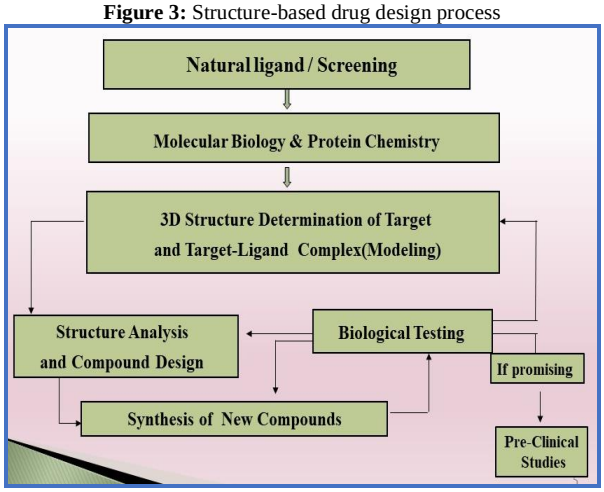
CADD Strategies

After analyzing various test compounds (obtained from natural or synthetic sources) few can be refused due to low activity, presence of toxicity or carcinogenicity, low feasibility for synthesis, inadequate efficiency etc. Consequently, only one in 100,000 researched molecules can be brought into the market.

Structure-Based Drug Design (SBDD)

Drug design based on receptor structure is the primary methodology used in drug design. A flow of the steps involved in this approach is described in Fig 3 [10]. Structure-based virtual high-throughput screening (SB-vHTS) is the tool used *in silico* to classify supposed hits of a huge library of compounds to targets of known structure, relies on comparing the small molecule's 3D structure with the putative binding pocket. SB-vHTS selects ligands predicted to bind a specific binding site instead of traditional HTS, which experimentally asserts a ligand's general ability to bind, inhibit, or modify the protein's function allosterically making screening of large compounds libraries feasible within a finite time scale. SB-vHTS similarly employs minimum protein and ligand conformational sampling, as well as a simplified estimation of binding energy [17].

Figure 3: Structure-based drug design process

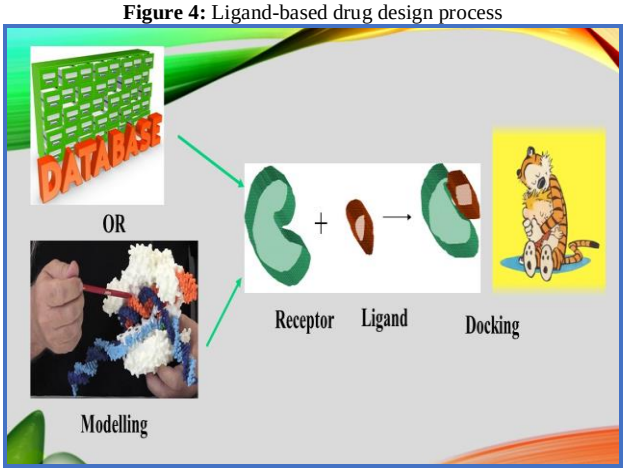


Ligand-Based Drug Design (LBDD)

This drug design technique emphases on ligands, including the study of ligands' interaction with a target. These methods involve the usage of generation of a 2D/3D chemical library of reference structures capable of interacting with the receptor (protein target) of interest. Because protein tertiary structure data is rarely accessible in LBDD, pharmacophore modelling is the first step in lead modification. Figure 4 depicts the flow of the steps involved in this method [4]. The ultimate purpose of LBDD is to show these chemical species in a fashion that preserves the most important physicochemical properties for their targeted interactions while discarding non-essential data [18].

The method does not necessitate knowledge of the target's structure, it is considered an indirect rather than a direct technique for drug development. The two main methods of LBDD are (1) collecting chemical species depends on their chemical characteristics' resemblance to a known active ingredient by utilizing a similarity metric, or (2) the construction of a QSAR model that supports us in predicting the biological activity of a chemical structure. LBDD approaches, unlike SBDD approaches, can be used in situations when the biological target structure is unknown [19].

Figure 4: Ligand-based drug design process



Steps and Software used for CADD

Target Protein molecules

Generally, the drug-receptor is the target protein molecule, categorized into enzymes, ion channels, and transporters. The precise 3D structures of a variety of membrane-bound proteins are still unknown. So, protein tertiary structure modeling is a perfect alternative approach for deciding the protein tertiary structure. Many specially designed software programs would allow detailed analysis of potential target molecules' target structure and dynamics for future aspects. These approaches lead to new challenges in validating and calibrating bio-simulation methods [20-23]. By experimenting with new methods and drug molecules, the initial step is to define and validate suitable targets. The rate of finding and exploration of novel targets is improving thanks to a combined strategy of Support Vector Machines and in-silico processes [21, 24].

Sources of dataset

Accessibility of data is the key to a successful drug research and development program. Scientific literature and case reports collect vast quantities of biological sequences, organic molecules, and related knowledge is stored in several cloud databases including PubMed [25], Embase [26], Google Scholar [27], Google patents [28], Clinicaltrials.gov [29] etc.

Small molecule databases

Databases for small molecules play a significant role in data collection for scientific exploration. Enormous compound libraries include the vast number of compounds approved by the FDA. All these databases have useful knowledge of organic products, carbohydrates, enzymes, chemical processes, and reactants. PubChem [30], Zinc [31], Chem spider [32], Drug bank [33], and others are examples of small-molecule databases, as illustrated in Table 2.

Sources of biological data

The human and other model organisms' genome sequencing has provided ever more significant data important to human disease study. Few of those sources of data are illustrated in Table 2 [34-36]. Swiss-Prot KB [37] and Protein Information Resource

[38] are databases that contain annotated protein sequences and functions. Swiss-Prot now has 563552 reviewed protein sequences [37]. PDB is the world's most comprehensive archive of biological macromolecular tertiary structural data. A total of 170,172 biological macromolecular structures have been deposited in PDB as of October 2020 (Table 2) [39].

Table 2: Some databases for small molecules and biologicals

Type	Database Name
Small molecule databases	Zinc Database, Zinc15Database, PDB, JChemfor Excel, Chemdiff, ChEMBL, Binding MOAD, Bingo, TTD, Drug Bank, PD Bbind,
Chemical structure representations	Chem Draw, ACD/Chem Sketch, Ketcher, jsMol Editor, UCSF Chimera, Open Structure, Pymol, InChI, DaylightSMILES, Marvin Sketch, TriposMol2, Corina, OpenBabel, Indigo, BINANA, DSV isualizer
Molecular Modeling	CHARMM, GROMACS, Swiss Side Chain, Amber, Swiss Param CHARMMing.org
Homology modeling	I-TASSER, Modeller, SWISS-MODEL, LOMETS, Robetta
Binding site prediction	MED-SuMo, 3DLigandSite, FINDSITE, CAVER, sc-PDB, CAST-p, Pocketome, PocketAnnotate
Docking	Auto dock, GOL, DOCK, Docking Server, 1-ClickDocking, Swiss Dock, COPICAT
Screening	Catalyst, Pharmer, Swiss Similarity, Pharma Gist, Blaster
Target prediction	PPB, Patch Search, CABRAKAN, Swiss Target Prediction SEA,
Ligand Design	GANDI, BREED, sc-PDB-Frag, SwissBioisostere, e-LEA3D,eDesign, GlideFragmentLibrary
Binding free energy estimation	BAPPL-Z server, Hyde, NN Score, X-score, BAPPL server
QSAR	CQSAR, ClogP/CMR, clogP, MOLEdb, OCHEM, CHEMDB/Datasets, Pattern Match Counter, E-Dragon
ADME Toxicity	Qik Prop, Gastro Plus, Vol Surf, Swiss ADME, ALOGPS

In addition to the abundance of knowledge from general-purpose biological databases, several specialist databases were also created which reflect existing empirical information about human biology and illness. Profiles of gene expression include hints of possible targets, which may be disease signatures. Databases such as ArrayExpress [17], Gene Expression Omnibus (GEO) [18], and CIBEX [19] are common depositories for this reason. In proteomics, 2D gel electrophoresis data is stored into tools like SWISS-2DPAGE [40] and GENBANK [41]. In contrast, data from mass spectrometry is accessible in databases like Global Proteome Computer Database and Open Proteomics Database [42], the MDL Metabolite database [43] and the METLIN database [44].

Cheminformatics and Bioinformatics

The new and growing field of chemoinformatic is the standard in practice for applying computer technology in chemistry including chemo-informatics, modelling, QSAR and calculation algorithms, database retrieval, etc [36].

Virtual Screening

It is a computer-assisted method for finding compounds that are likely to attach to the target molecule. These methods are divided into two categories: ligand-based screening and structure-based screening. Ligand selection is established on various criteria; like for a chemical ligand to be drug-like, it must follow the Lipinski rule of five. By using the above four factors, selective molecules are taken for further study. A selected drug-like compound is validated using *in-silico* docking study for its affinity towards its receptor [39].

Molecular Docking

It is a method to determine the affinity between ligand and active target protein binding sites in order to research ligand-receptor interactions. The ligand-receptor complex obtains the most energetically stable geometry by docking. Many scoring systems, such as dock score, potential energy for mean force score, and steric and electrostatic score, are used to indicate the minimal energy of interaction. This score aids in determining a ligand's receptor binding affinity [17].

Scoring Functions for Evaluation of Protein-Ligand Complexes

Possible ligand poses are created based on the structure of the protein during docking, and these binding and ligand poses are assessed using a score system [45]. Scoring functions are the most important part of docking and are divided into three categories [46]:

i. Determination of a ligand's binding mechanism and binding pocket on a protein [47]
ii. Prediction of total ligand-protein binding affinity in the context of lead optimization [48-49]
iii. Virtual screening, which involves exploring accessible ligand databases for the most effective drug leads [50].

Empirical, physics-based, machine learning-based, and knowledge-based scoring functions are the most often utilised for studying ligand-protein interactions in CADD [51] using software like SYBYL [52], DOCK [53], Schrodinger [54], Discovery Studio [55], Autodock vina [56], Autodock [57], etc.

Force-Field or Molecular Mechanics-Based Scoring Functions

Classic molecular mechanics is used to assess energy in force-field scoring functions [58]. These functions are based on parameters generated from experimental data and *ab-initio* mechanical measurements. The various programmes employ various force field settings, such as DOCK, which employs AMBER force fields in which the Lennard-Jones potential function defines van der Waals energy terms. Electrostatic conditions, on the other hand, account for coulombic interaction with a distance-dependent dielectric function [34].

Conformation Generation through CADD

Small molecule conformation creation is an important part of drug design and manufacture.

The physical and biological properties are controlled by various conformation orientations. One of such algorithms is Cyndi which is a multi-objective evolution algorithm-based method for bioactive molecular conformational generation and is highly accurate.

Cyndi searches the conformational space in constant time and regulates the geometric complexity and the accessibility of resources [59]. Another is Macro Model built into MaestroV7.5 (Schrodinger Inc.). That is different from Cyndi in terms of conformational space sampling depth, and the conformational cost [60, 61]. Examples of such algorithms are enlisted in Table 3.

Table 3: Examples of Conformational Search Algorithms

Systematic Search	Random Search
FRED	Auto Dock
FLOG	Ligand Fit
GLIDE	CDocker
DOCK	GOLD
EUDOC	Mol Dock
ADAM	Molegro Virtual Docker
SLIDE	PLANTS
eHiTS	EADock
FlexX	ICM

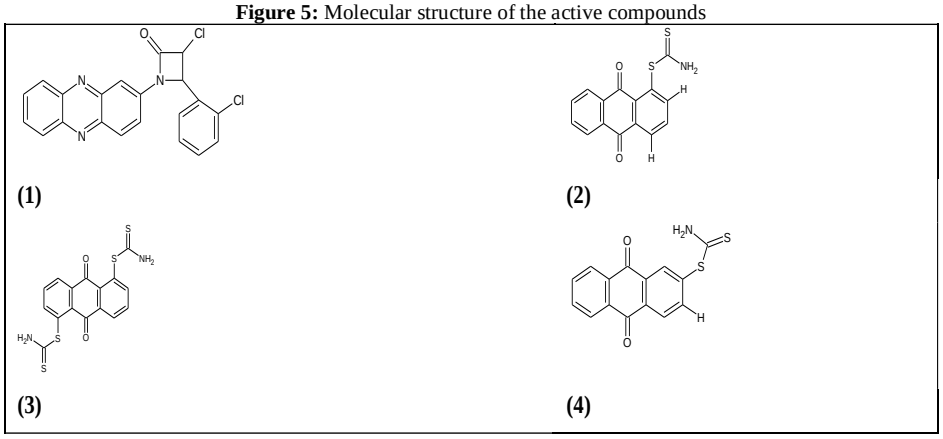
Role of CADD in the DDP

CADD has successfully enhanced the discovery of several innovative medications, making it a watershed moment in this field [62]. These techniques have been used to assess the biological activity of a variety of compounds. Few of such studies are summarized in this section.

In a study, Kale *et al.* evaluated 2-phenazinamines for their anticancer potential and selectivity for BCR-ABL Tyrosine kinase receptors using computational methods. For this purpose, Autodock 4.2 and VLife MDS 4.3 tools were used. Based on results, 3-chloro-4-aryl-1-(phenazine-7-yl) azetidin-2-ones **(1)** were obtained as lead for synthesis. The docking studies showed binding affinity of some derivatives was about >30% higher than the binding energy of the standard drug imatinib (Fig 5) [63].

Another study was carried out by Stasevych *et al.*, in which the anticancer activity was evaluated using PASS computer program and PharmaExpert software. The dithiocarbamate derivatives of 9,10-anthracenedione were further evaluated *in vitro* using cancer cells of the prostate (PC3), human lung (A549), human breast (MCF7) and colon (HT29). The anticancer activity observed with PASS computer program with a probability >30% was also confirmed by the *in vitro* experimental work. The structure of active compounds **(2, 3 and 4)** are shown in Fig 5 [64].

Figure 5: Molecular structure of the active compounds



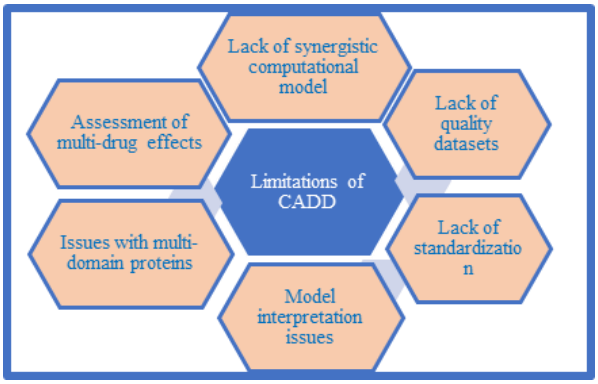
In silico analysis of 2-((pyridin-3-yloxy)methyl)piperazine derivatives using Auto-Dock 4.2.5.1 for evaluating their anti-inflammatory activity was carried out by Purohit *et al.*, using software Tripos SYBYL X, the homology model of the receptor protein, α7 nicotinic acetylcholine, was generated in SWISS MODELLER. The score derived from docking analysis was then correlated with experimental pIC_{50} values for *in-silico* validation of the developed CoMFA model and the obtained correlation was good. The results suggested an optimal 3D-QSAR with CoMFA model for further evaluating new chemical entities based on piperazine skeleton [65].

Merits of CADD

- CADD is a less time-consuming technique, and it has replaced the traditional experimentation that required animal and human models [66].
- The technique is also cost-effective [67].
- CADD plays an essential role in lowering the risk of drug resistance [1].
- It is an automatic and rapid process [68].
- Using *in-silico* filters for evaluating drug-likeness and pharmacokinetic parameters, it removes molecules with unwanted features [69].
- It is feasible to learn about the drug/ligand and receptor interaction pattern using CADD technologies.
- Additionally, failures at the last step of the drug development process may be decreased [12].

Limitations associated with CADD are shown in Figure 6.

Figure 6: Limitations of CADD



Prospects

CADD is a powerful tool in the field of drug discovery, and it is projected to be very valuable in the creation of pharmaceuticals. Pharmaceutical businesses can use *in-silico* approaches to assist them compete against companies that use traditional methods. With the implementation of CADD in the drug development process, researchers may always hope for improvement in the area of drug discovery. In recent years many impressive results have been achieved with the implementation of CADD which has paved a path for further development soon.

CONCLUSIONS

Computer-aided drug design is a complex discipline involving various approaches and methods of science. Though *in-silico* tools cannot completely replace the tests performed in laboratories, the computational technique accelerates and optimizes the discovery and development of new active compounds. The primary goal of computer-aided drug design is to find new ligands that are likely to bind with target proteins. CADD also helps to reduce the number of compounds that must be manufactured and analysed for biological potential, making the drug development process less time-consuming and cost-effective. In this review, the authors tried to compile major areas of CADD including applications in drug development. Nevertheless, efforts are required to be made towards development of new *in-silico* tools and advancement of existing tools in order to make this technique an advanced technology in drug discovery and development.

Abbreviations

CADD	Computer-Aided Drug Designing
DDP	Drug Discovery Process
EMB	European Molecular Biology
HIV	Human immunodeficiency virus
PLC	Protein Ligand Complex
SBDD	Structure-Based Drug Design
LBDD	Ligand-Based Drug Design
SB-vHTS	Structure-based virtual high-throughput screening
QSAR	Quantitative structure-activity relationship
PDB	Protein Data Bank
MOAD	Mother Of All Database
BINANA	BINding ANAlyzer
KKB	Kinase Knowledgebase
DNP	Dictionary of Natural Products
CASTp	Computed Atlas of Surface Topography of proteins
QSPR	Quantitative Structure-Property Relationship

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Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not Applicable

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