GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

Application of computer-aided drug design in drug discovery and development: Updating knowledge

Natolotriniavo Tendrinarisoa RANDRIAMAMISOLONIRINA [1, *], Olivier Fridolin MAMINIAINA [1, 3, 4], Andriambandaina Abel ANDRIANTSIMAHAVANDY [2] and Mirantsoa Suzanne RAZAFINDRAFARA [1, 3]

[1] *Department of Research and Quality Control, Malagasy Institute of Veterinary Vaccines, Madagascar.*
[2] *Department of Fundamental and Applied Biochemistry, Faculty of Science, University of Antananarivo, Madagascar.*
[3] *Department of Zootechnical, Veterinary and Fish Research, National Center for Applied Research on Rural Development, Madagascar.*
[4] *Department of Veterinary Science and Medicine, Faculty of Medicine, University of Antananarivo, Madagascar.*

GSC Advanced Research and Reviews, 2024, 21(01), 209–227

Publication history: Received on 28 August 2024; revised on 14 October 2024; accepted on 16 October 2024

Article DOI: https://doi.org/10.30574/gscarr.2024.21.1.0360

Abstract

Coronavirus (CoV) diseases are widespread throughout the world and have caused considerable socio-economic disruptions. For this reason, efforts have been made to develop a direct or indirect antiviral drugs against these diseases. However, no specific antiviral drug has yet been approved by the Food and Drug Administration (FDA) for CoV infections. Thus, the challenge in discovering therapeutic molecules against these infections remains pertinent. Computer-aided drug design (CADD) is one of the modern techniques for drug discovery and development. It accelerates the process, minimizes costs, and reduces research time.

In this article, we present the three CADD approaches, namely structure-based drug discovery (SBDD), ligand-based drug discovery (LBDD) and high-throughput virtual screening (HTVS). The different methods used in these three approaches CADD, such as molecular modelling, target structure analysis, molecular docking, molecular dynamics simulation, pharmacophore modelling, quantitative structure-activity relationship (QSAR), ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS) are detailed. In addition, the bioinformatics tools and databases commonly used in these different CADD techniques are also described.

Keywords: CADD; SBDD; LBDD; HTVS; Bioinformatics; Coronavirus

1. Introduction

Coronaviruses (CoV) are spherical, enveloped viruses with a crown-like structure with an average diameter of 80-220nm [1]. The term coronavirus comes from this crown- like structure, meaning « *corona* » in Latin [2]. CoV composed of four structural proteins: the spike glycoprotein (S), the membrane protein (M), the envelope protein (E), and the nucleocapsid protein (N). In Bétacoronavirus within the subgenus Embecovirus, a fifth glycoprotein called Hemagglutinin-Esterase is also observed [3]. Inside the envelope sits the viral genome, which consists of single-stranded positive-sense RNA of 26 to 32kb in size [4]. This genome is encapsidated in the N protein, forming a helically symmetrical ribonucleoprotein complex [1].

CoV infect a wide range of hosts and mainly cause respiratory or enteric diseases, but also neurological diseases or hepatitis in some cases [5]. They trigger serious epidemics involving considerable deaths in humans and animals [6, 7]. In poultry, a CoV called *Infectious Bronchitis Virus* (IBV) is responsible for avian infectious bronchitis, a highly contagious

* Corresponding author: RANDRIAMAMISOLONIRINA Natolotriniavo Tendrinarisoa

disease and a major problem for poultry production in several countries [8]. In swine, several porcine CoV were identified, including *Transmissible gastroenteritis virus* (TGEV), *Porcine epidemic diarrhea virus* (PEDV), *Porcine respiratory virus* (PRV), *Porcine hemagglutinating encephalomyelitis virus* (PHEV), *Porcine deltacoronavirus* (PDCoV) and *Swine acute diarrhoea syndrome coronavirus* (SADS-CoV) [9]. These are responsible for considerable economic losses for pig farmers [10].

Given this scale and severity of CoV infections, vaccination remains the best and most appropriate control strategy. However, the existence of high mutation rates in RNA viruses such as CoV [11] has often rendered vaccines ineffective even before their use. In addition, the plasticity of the CoV genome generates numerous variants, making CoV an agent with high evolutionary potential [12-14]. Moreover, the search for direct-acting antiviral agents against CoV infections is an ideal option when vaccines are lacking. Nevertheless, the development of drugs, like all pharmaceutical product development, is a complex process that takes a long time and requires a considerable investment [15]. It takes 10 to 15 years and several thousand dollars to bring a drug to market [16, 17]. These procedures will never be able to control infections in the event of a new epidemic outbreak in humans or an epizootic in animals.

Computer aided drug design (CADD) is a new technique for developing a drug using a computer. This method will reduce the time and cost required for drug development by 50% [18]. In fact, the pharmaceutical stage, which consists of searching for and identifying molecules that are active on target pathogens, will be reduced by applying CADD. In addition, the use of CADD can shorten experimental studies by guiding appropriate decisions concerning the preclinical (study of efficacy in the laboratory) and clinical (study of efficacy *in vivo*) research stages of drugs. In other words, this method can be used in the prevention and long-term control of emerging diseases such as CoV infections. As a research institution, we have already contributed to the fight against COVID-19, using our expertise in bioinformatics to validate the knowledge obtained from ethnobotanical surveys through *in silico* analysis of *Artemisia annua* [19] and *Cinnamosma fragrans* [20].

This review provides background information and a detailed overview of the CADD method, highlighting commonly used databases and bioinformatics tools. It has been written by summarizing new knowledge on the use of the *in silico* method in drug discovery and development. An application of this method in the development of drugs against *Coronavirus disease 2019* (COVID-19), a CoV infection responsible for a pandemic in 2020, is also reported.

2. Overview of the CADD

CADD approaches are widely used in the pharmaceutical industry [21, 22]. In drug development, they can act at several stages: (i) identification of targets, (ii) validation of targets, (iii) identification of leads (molecules with good affinity for the target of interest), (iv) optimization of leads, and (v) preclinical trials (Figure 1).

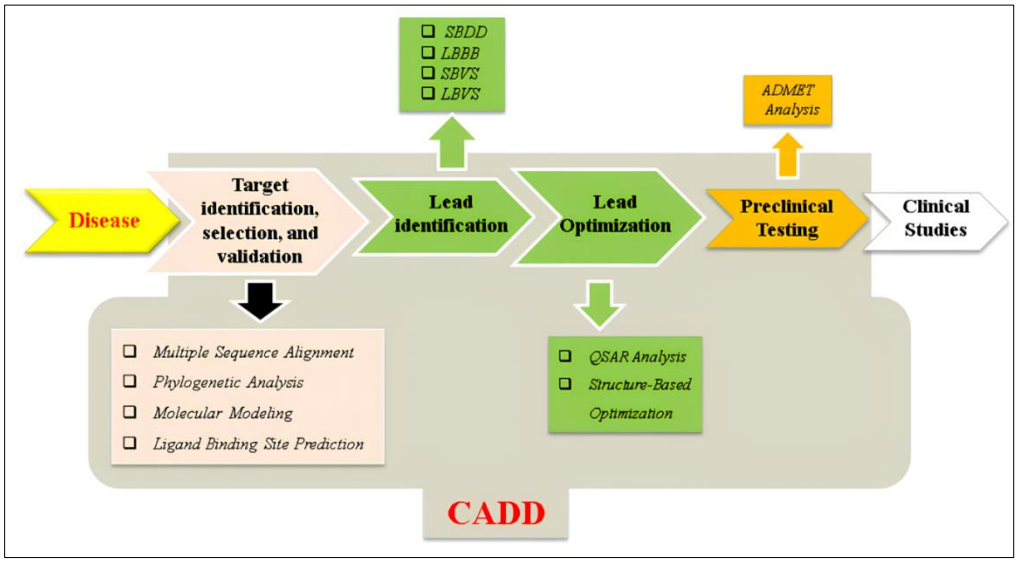

Figure 1 Application of CADD in drug discovery and development

CADD methods depend on the availability of structures for the targets and their ligands. In fact, two strategies called 'direct design' and 'indirect design' are available. In direct design, the structural characteristics of the target are considered. In contrast, for indirect design, the structural characteristics of the ligands are considered [21]. Based on these two strategies, three CADD approaches are currently available: (i) structure-based drug design (SBDD); (ii) ligand-based drug design (LBDD); and (iii) high-throughput virtual screening or HTVS (Figure 2). The following paragraphs describe these different methods in detail.

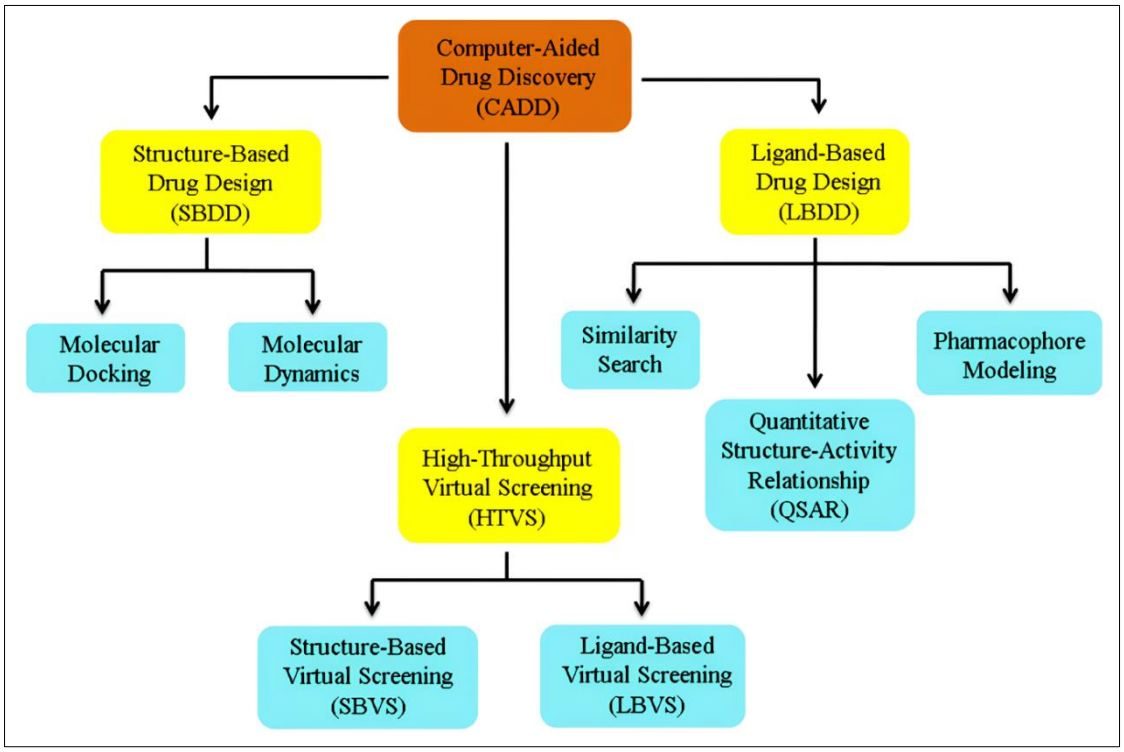

Figure 2 CADD methods

3. Structure-based drug design (SBDD)

SBDD is a CADD approach based on information found in the structure 3D of the target. It can be performed depending on the availability of this structure [23]. Hence, this method is used in the selection and optimization of lead molecules [16, 24].

The widely used SBDD methods include molecular docking and molecular dynamics simulations [17]. The steps of SBDD include: (i) target identification and selection, (ii) structural analysis of the ligand binding site on the selected target, (iii) preparation of the ligand library, (iv) analysis of the docking and scoring function, and finally (v) molecular dynamics simulation (Figure 3).

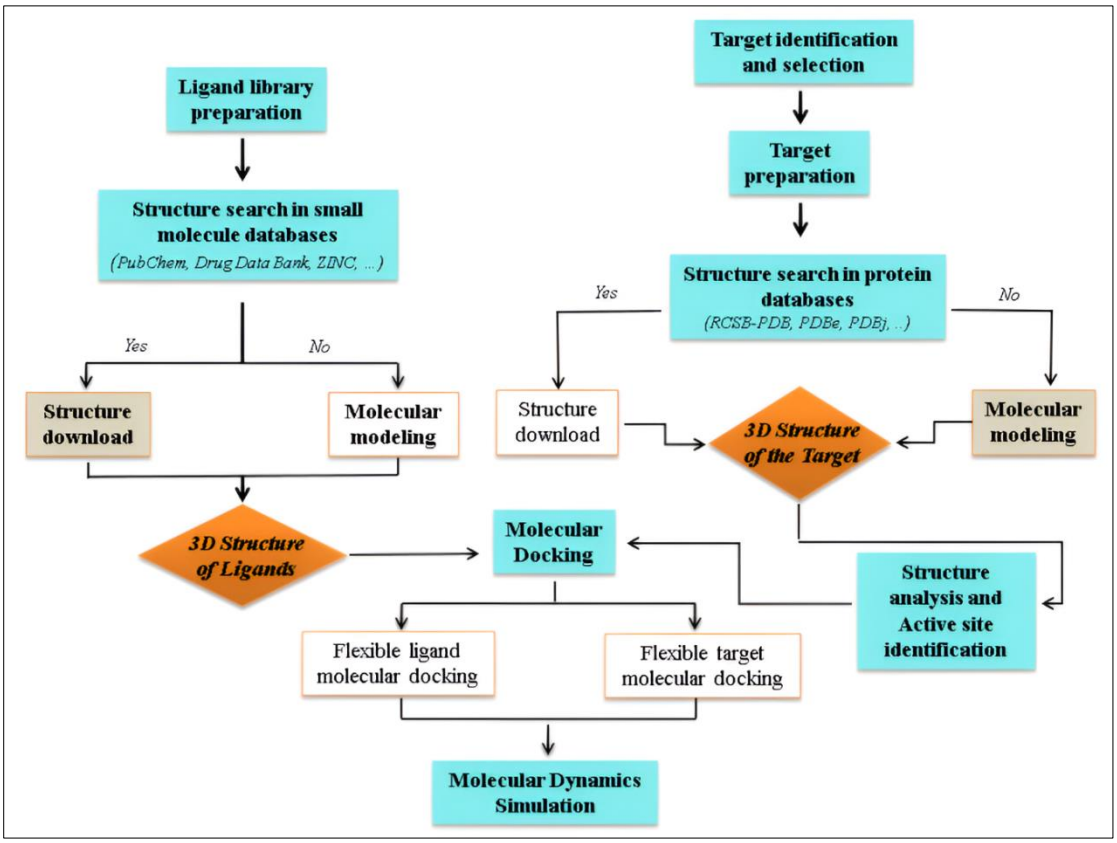

Figure 3 SBDD flowchart

3.1. Target identification and validation

SBDD processes are generally started by the identification and validation of the target molecule [25]. Target identification refers to the search for a biological target whose activity can be controlled by a drug. On the other hand, target validation consists of proving that a target is actually involved in the process in question and that regulation of this target may prove advantageous [26].

The identification of drug targets in drug research is a long and laborious task. It is also impossible to screen for all drug targets in a laboratory experiment. Therefore, bioinformatics methods such as comparative genomics [27], network-based methods [28], drug side-effect monitoring [29] and artificial intelligence [30] could be used.

The targets for drug discovery are generally proteins (membrane receptors, soluble proteins or enzymes). However, they can also be DNA or RNA [31]. In the case of protein targets, their structures are obtained using in vitro techniques such as X-ray crystallography, nuclear magnetic resonance and cryo-electron microscopy [32]. They are then stored in the structure databases incorporated in wwPDB [33], such as RCSB-PDB (https://www.rcsb.org/), PDBj (https://pdbj.org/) and PDBe (https://www.ebi.ac.uk/pdbe/). For genomics targets, various bioinformatics tools and methods are described in the review by [34].

3.2. Molecular modelling

If the structures of protein targets are not available in these databases of structures, molecular modelling methods can be used to predict their structure three-dimensionally (3D). Several methods of molecular modelling, including homology modelling, threading modelling and Ab initio or folding modelling are available [35]. In addition, online and offline bioinformatics tools are also available for molecular modelling, refining and visualizing the resulting structural models (Table 1).

Table 1 Examples of bioinformatics tools available for molecular modelling

Tools	Description	References
SWISS-MODEL	Homology modelling server	[36]
MODELLER	Software for homology modelling	[37]
I-TASSER	A threading based molecular modelling server	[38]
Rosetta	An *Ab initio* molecular modelling platform	[39]
3Drefine	A server for refinement of protein model structures	[40]
YASARA	A server for energy minimization using the YASARA force field	[41]

The selection of methods and tools used in molecular modelling depends on identity and similarity of target protein sequences to model protein sequences. These are available in databases such as NCBI (https://www.ncbi.nlm.nih.gov/) and UniProt (http://www.uniprot.org/). Furthermore, the selection of modelling methods also depends on the availability of homologous 3D structures of the target in the databases of protein structures (Figure 4).

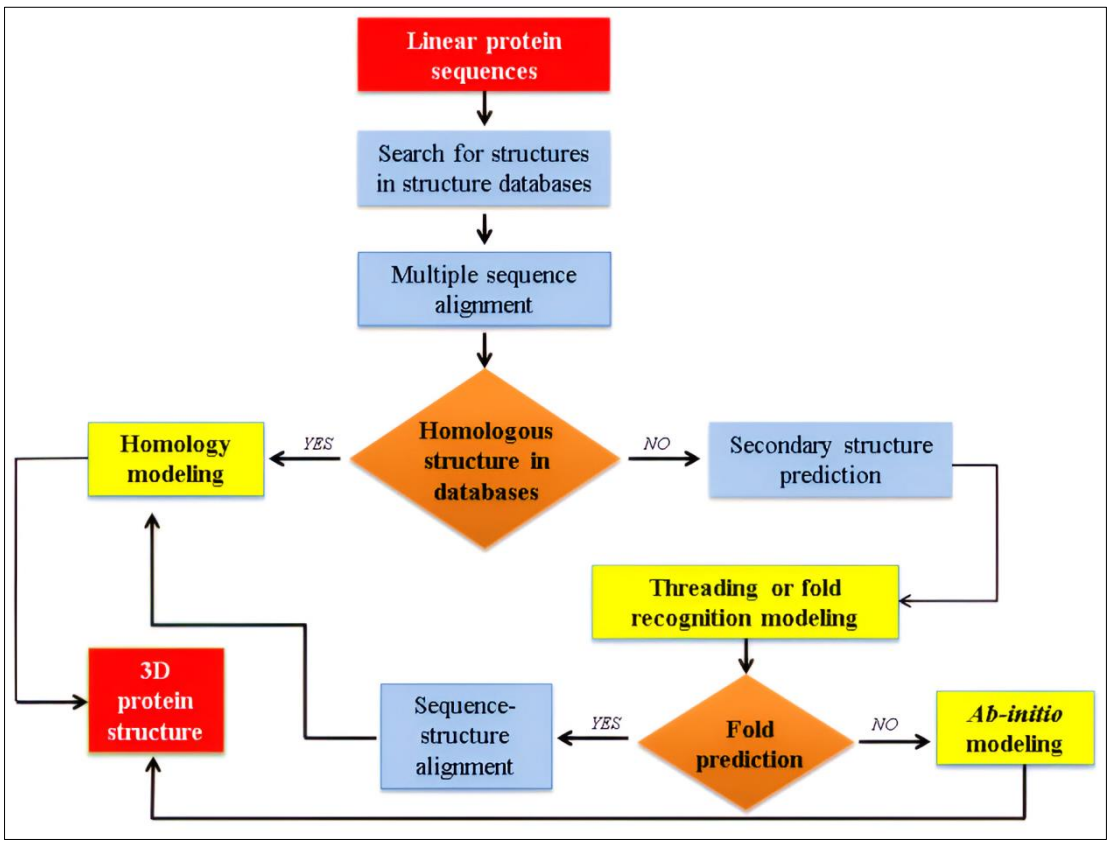

Figure 4 Methodical diagram of molecular modelling

Homology modelling is the most widely used in drug discovery [42]. It is based on the fact that protein structure is better conserved than their sequence, i.e. proteins with similar sequences have similar structures and small or medium changes in sequence can result in a small change in 3D structure [42]. The process of homology modelling involves seven steps: (i) model identification and selection, (ii) sequence alignments of targets and models, (iii) model construction, (iv) loop modelling, (v) side chain modelling, (vi) model optimization or refinement and (vii) validation and verification of model quality [43].

Several methods can be used to validate and check the quality of the 3D model obtained by molecular modelling. The stereochemistry of the model can be checked using tools such as PROCHECK [44] and WHAT_CHECK [45]. Spatial

characteristics can be validated using Verify3D [46]. Global quality and local quality for each model residue can be estimated using QMEAN server [47]. Other structure validation tools include MolProbity [48] and SAVES v6.0 [49-51].

3.3. Identification of active sites and analysis of target pharmacogability

After target identification and selection, the second step in SBDD is to examine the presence of a suitable active site or ligand binding site in the desired target. Obtaining this information is a prerequisite for molecular docking [52]. Active site analysis is performed in protein structure visualization software such as UCSF Chimera [53], Biovia Discovery Studio Visualizer [54], Swiss-PdbViewer [55]. In cases where the information on the active sites of the target is not available (for example, in the case of structures obtained by molecular modelling), a number of bioinformatics tools are also available for prediction (Table 2).

Table 2 Examples of bioinformatics tools for predicting ligand binding sites in target proteins

Tools	Description	Methods	References
Q-SiteFinder	Web server for identifying the location of ligand binding sites in a protein	Energy-based methods	[56]
3DLigandSite	Web server for predicting ligand binding sites	Structural model-based methods	[57]
LIGSITE^{csc}	Web server for predicting ligand binding sites in proteins	Surface-based methods using Connolly's surface and degree of conservation	[58]
PASS (Putative Active Sites with Spheres)	Web server for characterising regions embedded in proteins and identifying the potential positions of ligand-binding sites	Geometry-based methods	[59]
COACH	A metaserver for predicting protein-ligand binding sites	Hybrid methods	[60]
DeepSite	Web server for predicting protein binding sites	Machine learning methods	[61]

As well as identifying the binding site, it is also important to assess the the pharmacogability of the target. This is the probability that a target will be regulated by a small molecule drug [62]. Examples of methods for predicting target pharmacogability include SiteMap [63], DLID [64], DrugPred [65] and DoGSiteScorer [66].

3.4. Molecular docking

Molecular docking is one of the most widely used of SBDD methods [67]. With this method, it is possible to identify the molecules (or ligands) that interact strongly with the active site of the target. In addition, it helps to determine the most favourable ligand orientations in the target's active site [68]. A number of molecular docking tools can be used to generate the binding set and position of ligands in the active site of the target (Table 3).

Table 3 Bioinformatics tools available for molecular docking

Tools	Description	References
SwissDock	Web server for molecular docking between a target protein and a small molecule	[69]
AutoDock	Software for docking a small molecule to a known target structure	[70]
AutoDock Vina	A programme for molecular docking and virtual screening	[71]
AutoDockTools	Graphical interface for analysing the results of molecular docking analysis on AutoDock	[70]
HADDOCK 2.2	Software for a flexible docking approach for protein-protein, protein-nucleic acid and protein-ligand complexes	[72]
PatchDock and SymmDock	Protein-protein and protein-ligand docking server	[73]
PyRx	Software for virtual screening for computational drug discovery	[74]

Tools	Description	References
ClusPro	Protein-protein docking server	[75]

Molecular docking methods are classified into three categories: (i) rigid docking where the target and ligands are treated as rigid entities; (ii) flexible docking where the ligand and target are considered flexible; and (iii) flexible ligand docking where the ligand is considered flexible while the target is considered rigid [76]. Consequently, the docking procedures can be classified according to the degree of flexibility of the molecules involved in the calculation [68]. Nevertheless, the main procedures in these three methods are similar (Figure 5).

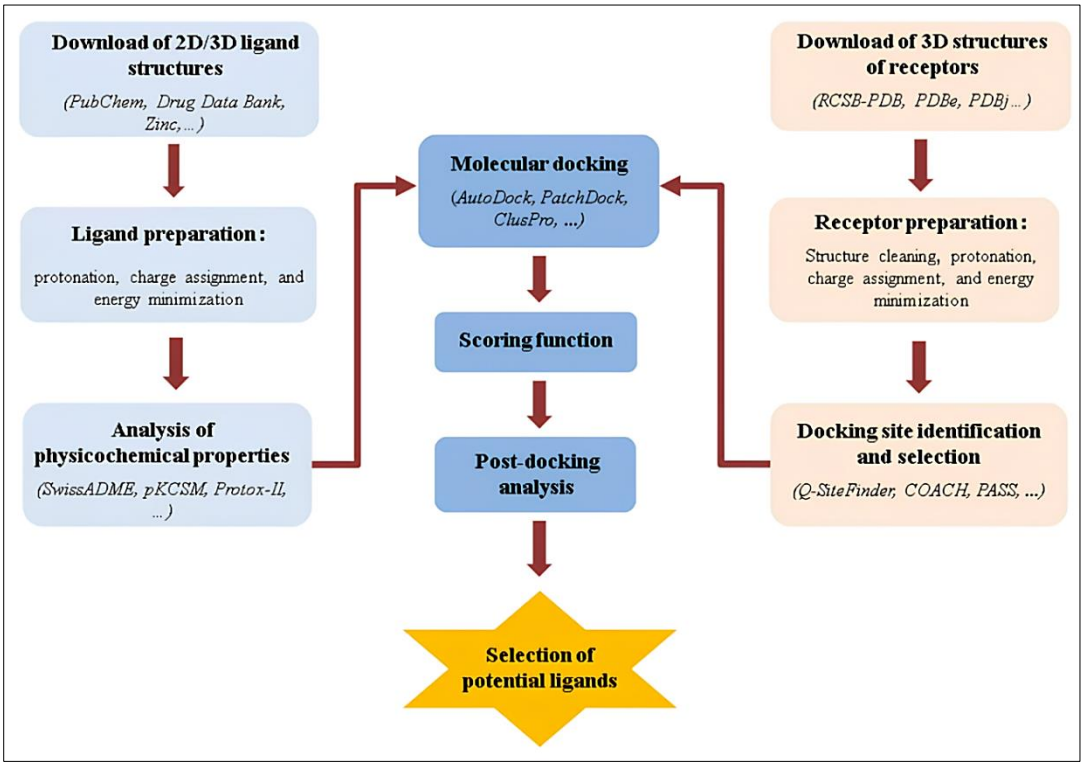

Figure 5 Principal process of molecular docking

3.5. Scoring functions

A molecular docking analysis can generate several conformations of target-ligand complexes. To classify these complexes, to differentiate valid versus invalid ligand binding modes and to estimate ligand binding affinities to the target, scoring functions are required [52]. Scoring functions are generally divided into three main classes: force-field-based, knowledge-based and empirical [77].

Force field scoring functions calculate target-ligand binding energy, using classical molecular mechanics such as van der Waals interactions, electrostatic interaction, bond stretching/bending/twisting energies, and solvation/de-solvation effects [78]. Examples of force-field based scoring functions include DOCK [79], MedusaScore [80], AutoDock [70], AutoDock Vina [71], MM-PBSA/ MM-GBSA [81] and DockTScore [82].

Empirical scoring functions estimate the binding affinity of a ligand to the target, combining energetic factors important for molecular interaction such as hydrogen bonds, hydrophobic bonds, steric hindrances and solvation/desolvation effects [83]. Examples of empirical scoring functions include LIDI [84], ChemScore [85], GlideScore [86], ID-Score [87], Lin_F9 [88].

Knowledge-based scoring functions measure the binding affinity of the docking complex by combining the values of the average force potentials (AFPs) between the atoms in the protein-ligand complex [89]. Examples include DrugScore CSD [90], PMF-Score [91], ITScoreDA [92], ITScore-NL [93].

Recently, consensus approaches to scoring functions have been developed. They combine different scoring functions to improve the probability of finding correct solutions [21]. Examples of consensus scoring are GFscore [94], SeleX-CS [95], KECSA [96], SMoG2016 [97].

3.6. Molecular dynamics simulation (MD)

MD provides comprehensive information on the molecular dynamics of targets and their potential interactions with ligands. With this technique, it is possible to determine the movement of targets and ligands at the atomic level and their specific interactions. Bound (stretching energies, bending angle, dihedral angle) and unbound (van der Waals force and electrostatic energies) atomic interaction potential energies are used to determine molecular dynamics. MD simulations are required for post-docking structural refinements and stability analysis of protein-ligand complexes. Several programs are commonly used for MD calculations. These include GROMACS [98], AMBER [99], GROMOS [100], NAMD [101] and CHARMM [102].

4. Ligand-based drug design (LBDD)

When the target of interest for drug discovery and development is unknown, or its 3D structure is not available, CADD can use another alternative approach, known as ligand-based drug design or LBDD. This technique exploits information contained in small molecules or ligands interacting with a drug target, to identify putative molecules that could have similar biological activities with known active molecules [24]. This information includes the binding affinities of ligands with targets, the structure and physicochemical properties of ligands [103]. Common techniques used in this approach include similarity searching, pharmacophore modeling and quantitative structure-activity relationships QSAR [104].

4.1. Similarity search

The ligand similarity search is based on the principle that physico-chemically similar compounds have similar biological activities. This method could therefore search for compounds similar to the compounds analyzed [105]. Indeed, similarity search is based on two descriptors including chemical fingerprints and physicochemical properties [104]. Chemical fingerprints are used to identify compounds that are structurally similar to the target active compounds, while physicochemical properties can be useful for identifying molecules with a new chemical structure but retaining the biological activity of the target active compounds.

To measure the degree of similarity between the compounds found and the target compounds, several methods such as the Tanimoto, Cosine, Hamming, Russel-Rao and Forbes indices are available [104]. In addition, offline and online bioinformatics tools such as Discovery Studio Visualizer [54], SEA server [106] and Swiss Similarity [107] are also available.

4.2. Pharmacophore modeling

Pharmacophore modeling is based on the fact that ligands with common chemical functions for similar targets have similar 3D conformations. An important prerequisite for the success of this method is knowledge of the pharmacophore characteristics of ligands that bind to the same protein target with a similar orientation [108]. Otherwise, the pharmacophore models obtained will not represent the correct mode of action and cannot be used in the identification of new active ingredients.

The most widely considered pharmacophoric features are: hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), hydrophobic zones (Hs); aromatic rings (AR), positively and negatively ionizable groups (PIs/NIs), metal coordination zones and XVOLs exclusion volumes [109]. The pharmacophore model-building steps are summarized in figure 6. Several bioinformatics tools are available and can be used freely for pharmacophore modeling. These include Pocket v.2 [110], PharmaGist [111], LigandScout [112] and ZincPharmer [113].

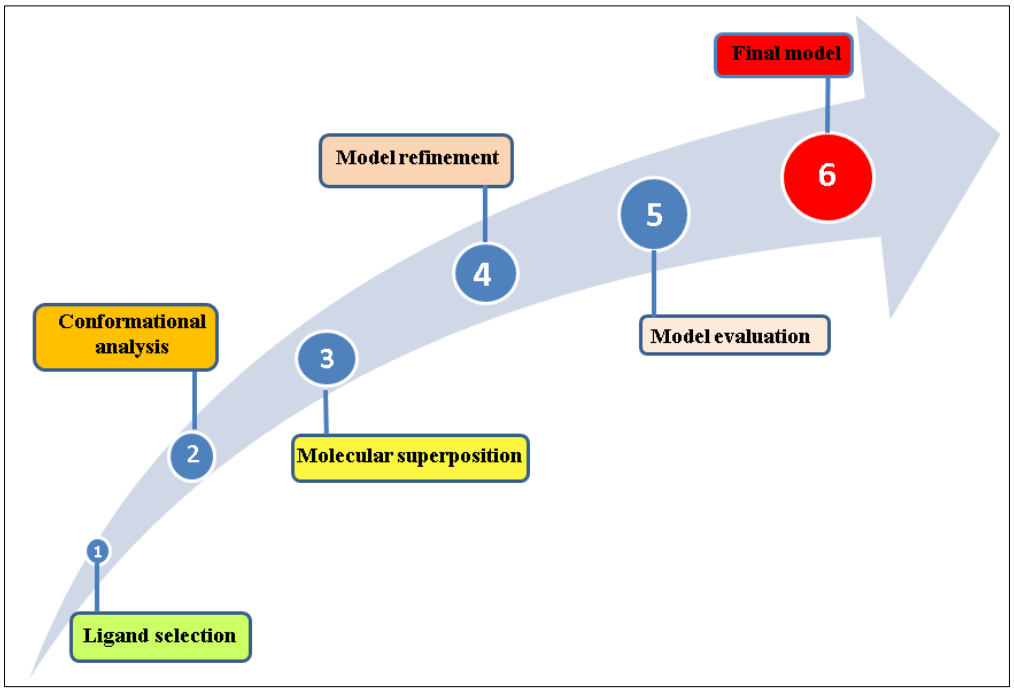

Figure 6 Pharmacophore modeling process

4.3. Quantitative structure-activity relationship (QSAR)

The QSAR relationship is one of the most popular approaches to LBDD. It uses statistical methods to study the relationship between the bioactivities of small molecules and their structural properties [114]. Bioactivities include therapeutic activities and adverse effects. In addition, structural properties correspond to physicochemical properties (Molecular weight, Number of atoms, Number of aromatic nuclei, Number of rotatable bonds, HBA, HBD, Molar refractivity, TPSA, Lipophilicity and Solubility), pharmacokinetic properties (Adsorption, Distribution, Metabolism, Excretion) and toxicological properties [115]. QSAR analysis steps involve: (i) dataset preparation, (ii) structural optimization, (iii) molecular descriptor selection and calculation, (iv) QSAR model development and finally (v) final model evaluation and validation [116, 117].

QSAR methods are classified as 1 to 6D QSAR. However, the 3D QSAR method is the most popular [118]. The latter correlates biological activity with non-covalent bonds around molecules [115]. Among 3DQSAR programs, the CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Molecular Similarity Indices Analysis) methods are the best known [119-121]. In addition, a number of tools are available for QSAR model development. These include ChemSAR [122], 3D-QSAR [123] and Cloud 3D-QSAR [124].

5. High-throughput virtual screening (HTVS)

HTVS is another CADD approach that has attracted considerable interest in pharmaceutical research as a productive and cost-effective technology. HTVS is used to select compounds most likely to show biological activity against a target of interest from small molecule structure databases [125]. In addition, it can predict the specific pharmacodynamic, pharmacokinetic and toxicological properties of these compounds based on their structural and physicochemical properties [126]. In this way, HTVS can be used to help identify lead molecules and optimize or improve their physicochemical properties [125]. Compared with other CADD methods, virtual screening can quickly separate active from inactive samples based on a large number of samples [127].

Structure databases have already been created to store the 2D/3D structures of these molecules. These include the Protein Data Bank [128], PubChem [129], ChEMBL [130], ChemSpider [131], Zinc [132], Drugbank [133] and NPASS [134].

Depending on the availability of targets or ligands, virtual screening methods can be classified into structure-based virtual screening (SBVS) and ligand-based virtual screening or LBVS [52]. In addition, studies have proposed combining

these two methods to overcome their individual advantages and weaknesses [135, 136]. Figure 7 summarizes the general process of SBVS and LBVS.

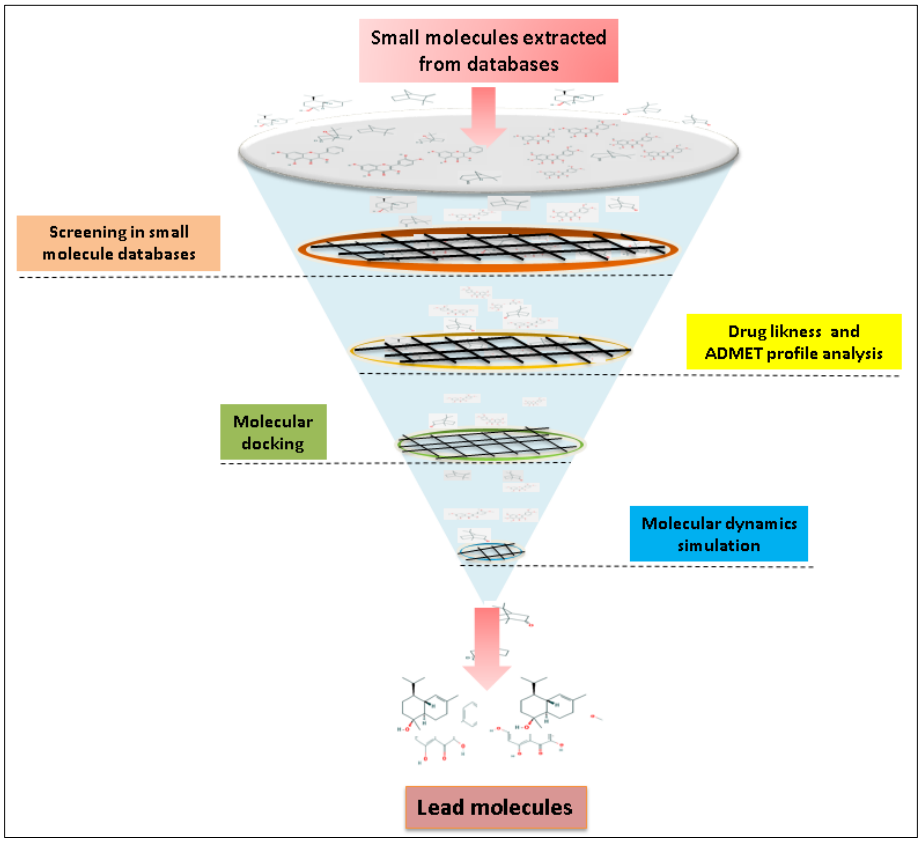

Figure 7 High-throughput Virtual Screening process

5.1. Structure-based virtual screening (SBVS)

SBVS identifies putative hits among hundreds of thousands of compounds with known structure targets. Here, a target is "screened" against a library of molecules and the binding affinities of these molecules to the target are estimated using molecular docking and the use of scoring functions [137]. Thus, molecules are ranked according to their affinity with the target, and those with the most promising affinity are selected at the end of screening [126]. SBVS is generally based on molecular docking [67]. Thus, a prerequisite for using SBVS is the availability of 3D structure of the target and ligands.

5.2. Ligand-based virtual screening (LBVS)

LBVS is a good option for identifying lead molecules if the target's 3D structure is unknown, or if it is difficult to perform virtual screening using structure-based methods [138].

LBVS is based on structural information and the physicochemical properties of ligands. These criteria are evaluated according to the principle of molecular similarity [139]. This principle states that structurally similar small molecules are likely to have similar biological properties and activities [140].

5.3. Optimization of lead molecules

In addition to identifying lead molecules, HTVS can also help optimize them. This step can reduce the number of compound that need to be synthesized and tested in clinical trials. Optimization involves analysis of the chemical structures and physicochemical properties of ligands [22]. The latter make it possible to assess the drug-like nature of lead molecules [141]. Since then, various drug similarity rules based on simple molecular properties have been developed, such as those proposed by Lipinski and colleagues [142], Ghose and colleagues [143], Muegge and colleagues [144] and Veber and colleagues [145]. These rules suggest that compounds falling within their ranges are predicted to be "drug-like".

In addition, optimization of lead molecules also includes analysis of pharmacokinetic profiles such as absorption, distribution, metabolism, excretion and toxicity (ADMET). Studies have shown that poor pharmacokinetic and toxicological properties are the most important causes of costly failures in late-stage drug development [146, 147]. Thus, lead optimization focuses largely on the analysis of ADMET parameters. These parameters include solubility, intestinal absorption, Caco-2 permeability, human bioavailability, membrane glycoprotein binding, volume of distribution, cytochrome P450 metabolisms, half-life, renal excretion, total clearance, toxicities, lethal dose at 50% in rats or mice [148].

Numerous bioinformatics tools are available and can be used for drug similarity assessment and ADMET prediction of lead molecules. These include PreADMET [149], SWISS ADME [150], pkCSM [151] and AdmetSAR 2.0 [152].

6. Application of CADD in the discovery and development of drugs for COVID-19

The CADD techniques described in the preceding paragraphs are used in the search for drugs to combat COVID-19 [153]. Here are a few examples of research work that has exposed some of these methods : Alrasheid and colleagues evaluated biologically active compounds present in medicinal plants as potential COVID-19 inhibitors, using molecular docking methods [154]. Enmozhi and colleagues evaluated the compound Andrographolide from Andrographis paniculata as a potential inhibitor of SARS-CoV-2 Mpro through *in silico* methods such as target analysis, molecular docking, toxicity prediction and ADME prediction [155]. Arwansyah and colleagues used homology modeling, molecular docking and molecular dynamics simulations to identify drugs that inhibit the papain-like protease (PLpro) of SARS-CoV-2[156]. Kumar and colleagues combined pharmacophore-based virtual screening, molecular docking and molecular dynamics simulation to identify potential ligands that inhibit SARS-CoV-2 main protease (Mpro) from the natural products database. [157]. Idris and colleagues used the pharmacophore modeling approach, coupled with molecular docking and molecular dynamics simulation to identify promising molecules against human TMPRSS2 [158]. Zarezade and colleagues sought to discover specific inhibitors of ACE2 and the main protease through 3D-QSAR pharmacophore modeling, virtual screening, molecular docking, de novo ligand design, molecular dynamics simulation, free energy profiling and QM-MM techniques [159]. Ferraz and colleagues used LBVS and SBVS techniques to identify three drugs approved as promising inhibitors of the major SARS-CoV-2 protease [160].

6.1. Potential molecular targets for the development of antiviral drugs against COVID-19

All viral proteins involved in SARS-CoV-2 replication are potential targets for drug discovery against COVID-19 [161]. These include structural and non-structural proteins such as the viral spicule (S), envelope protein (E), membrane protein (M), nucleocapsid protein (N), main protease or 3CLpro protease (nsp5), PLpro (nsp3), RNA-dependent polymerase (RdRp, nsp12), helicase (nsp13), Exoribonuclease (ExoN, nsp14), endoribonuclease (nsp15), 2′-O-methyltransferase or nsp16 [17]. Other non-enzymatic viral proteins are also potential targets [162].

In addition to these viral proteins, some approaches have also targeted host proteins such as ACE2, TMPRSS2, furin and cathepsin L and B [163]. In addition, targets associated with the host immune response have also been proposed [162].

6.2. Repositioned drugs and phytochemicals identified by CADD techniques as part of COVID-19

Several attempts have been made to investigate the repurposing of antiviral drugs approved for their health-promoting properties and their ability to boost the immune system against SARS-CoV-2. As a result, antivirals such as Lopinavir, Ritonavir, Remdesivir, Umnifenovir, Oseltamivir, Favipiravir, Chloroquine and Hydroxychloroquine are being repurposed for the treatment of COVID-19 [161]. Other drugs are also proposed by the CADD computational method, but they are not tested experimentally and/or clinically [153].

In addition, attempts have been made to identify chemical compound from medicinal plants that could be used in the development of drugs against COVID-19. As a result, several families of phytocompounds from numerous medicinal plants have been identified. Review articles by Jamiu and colleagues [164], Mousavi and colleagues [153] and Rani and colleagues [165] exposed several of these molecules.

7. Conclusion

The CADD method is widely used in the pharmaceutical industry for drug development. In this method, three approaches are available: SBDD, LBDD HTVS. SBDD uses molecular docking methods and molecular dynamics simulation to select and optimize lead molecules or molecules with good affinity for targets of interest. The structures of these targets can be obtained experimentally or modeled by molecular modeling methods, while LBDD uses active

ligands that can bind to the target. As for HTVS, they enable the selection of a large number of compounds most likely to show biological activity against a target of interest, using small molecule databases. They can also be used to optimize lead molecules, by analyzing their pharmacodynamic, pharmacokinetic and toxicological properties.

The CADD method has already been used in the search for drugs against COVID-19, targeting structural or non-structural viral proteins (spicule, envelope protein, 3CLpro, PLpro, RdRp, etc.) and host proteins (ACE2, TMPRSS2, furin and cathepsin L and B). These studies led to the selection of various existing antivirals (Lopinavir, Favipiravir, Chloroquine, Hydroxychloroquine, etc.) for the treatment of COVID-19. Chemical compounds from medicinal plants have also been identified as effective antivirals against COVID-19.

This information provides an essential foundation for users wishing to enter the field, and guides researchers working in the field, such as biochemists and pharmacists, in the choice of CADD approaches to adopt, depending on data availability. In the long term, it will also provide a means of responding rapidly and effectively to emerging or re-emerging diseases in humans or animals, whether CoV infections or other types of contagious disease. In the future, more in-depth use of these methods on a disease-specific basis is required. In addition, the development of a metadata or website bringing together all these bioinformatics tools for drug development is also envisaged.

Compliance with ethical standards

Acknowledgments

We would like to thank Malagasy Institute of Veterinary Vaccines (IMVAVET) for providing the equipment needed to carry out this study.

Disclosure of conflict of interest

The authors declare no competing interests.

References

[1] Holmes KV. SARS-associated coronavirus. N Engl J Med, 2003; 348(20):1948-1951.

[2] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al*. Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020; 382(13):1199-1207.

[3] Woo PCY, Huang Y, Lau SKP, Yuen KY. Coronavirus genomics and bioinformatics analysis. Viruses. 2010; 2(8):1804-20.

[4] Su S, Wong G, Shi W, *et al*. Epidemiology, Genetic Recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016; 24(6):490-502.

[5] Zhou Z, Qiu Y, Ge X. The taxonomy, host range and pathogenicity of coronaviruses and other viruses in the Nidovirales order. Anim Dis. 2021; 1(1):5.

[6] Jackwood MW. Review of infectious bronchitis virus around the world. Avian Dis. 2012; 56(4):634-641.

[7] Song D, Park B. Porcine epidemic diarrhoea virus: a comprehensive review of molecular epidemiology, diagnosis, and vaccines. Virus genes. 2012; 44(2):167-75.

[8] Cook JK, Jackwood M, Jones RC. The long view: 40 years of infectious bronchitis research. Avian Pathol. 2012; 41(3):239-50.

[9] Zhou L, Li QN, Su JN, Chen GH, Wu ZX, Luo Y, *et al*. The re-emerging of SADS-CoV infection in pig herds in Southern China. Transbound Emerg Dis. 2019; 66(5):2180-83.

[10] Martelli P, Lavazza A, Nigrelli AD, Merialdi G, Alborali LG, Pensaert MB. Epidemic of diarrhoea caused by porcine epidemic diarrhoea virus in Italy. Vet Rec. 2008; 162(10):307-10.

[11] Maminiaina OF, Razafindrafara MS. History of epizootics, epidemics and evolution of coronaviruses. International journal of infectious diseases and therapy. 2021; 6(4):132-45.

[12] Becares M, Pascual-Iglesias A, Nogales A, Sola I, Enjuanes L, Zuñiga S. Mutagenesis of coronavirus nsp14 reveals its potential role in modulation of the innate immune response. J Virol. 2016; 90(11):5399-414.

[13] Karamitros T, Papadopoulou G, Bousali M, Mexias A, Tsiodras S, Mentis A. SARS-CoV-2 exhibits intra-host genomic plasticity and low-frequency polymorphic quasispecies. J Clin Virol. 2020; 131:104585.

[14] Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL*, et al*. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. J Mol Biol. 2003; 331(5):991-1004.

[15] Mohs RC, Greig NH. Drug discovery and development: Role of basic biological research. Alzheimers Dement. 2017; 3(4):651-57.

[16] Batool M, Ahmad B, Choi S. A structure-based drug discovery paradigm. Int J Mol Sci. 2019; 20(11):2783.

[17] Gurung AB, Ali MA, Lee J, Farah MA, Al-Anazi KM. An updated review of computer-aided drug design and its application to COVID-19. Biomed Res Int. 2021; 2021:8853056.

[18] Xiang M, Cao Y, Fan W, Chen L, Mo Y. Computer-aided drug design: lead discovery and optimization. Comb Chem High Throughput Screen. 2012; 15(4):328-37.

[19] Randriamamisolonirina T, Andriamaroarison Ando T, Razafindrafara Mirantsoa S, Andriantsimahavandy Andriambadanaina A, Rakotosaona R, Ramanitrahasimbola D, et al. Screening of secondary metabolites in Artemisia annua as potential inhibitors of coronavirus proteases by *in silico* approaches. Advances in bioscience and bioengineering. 2021; 9(4):96-110.

[20] Randriamamisolonirina T, Maminiaina OF. Molecular docking study of seventy-six phytomolecules from sixteen aromatics medicinal plants as promising inhibitors of five non-structural proteins of SARS-CoV-2. GSC Biological and pharmaceutical sciences. 2022; 20(3):227-50.

[21] Das P, Saha P, Abdul A. A review on computer aided drug design in drug discovery. World Journal of Pharmacy and Pharmaceutical Sciences. 2017; 6(7): 279-91.

[22] Barrawaz AY. Computer aided drug design: a mini-review. Journal of medical pharmaceutical and allied sciences. 2020; 9:2584-91.

[23] Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015; 20(7):13384-421.

[24] Dar K, Bhat A, Amin S, Hamid R, Anees S, Anjum S, *et al*. Modern computational strategies for designing drugs to curb human diseases: A prospect. Curr Top Med Chem. 2018; 18(31):2702-19.

[25] Anderson AC. The process of structure-based drug design. Chem Biol. 2003; 10(9):787-97.

[26] Hoffman HI, Guo JA, Hwang WL. Chapter 8 - Drug discovery. In: Eltorai AEM, Bakal JA, Kim DW, Wazer DE, eds. Translational radiation oncology: Academic press; 2023. p. 39-43.

[27] Zhang X, Wu F, Yang N, Zhan X, Liao J, Mai S, *et al*. In silico methods for identification of potential therapeutic targets. Interdiscip Sci. 2022; 14(2):285-310.

[28] Jayachandran P, Ilango S, Paital B, Bhanja S, Nirmaladevi R. Approaches for network based drug discovery. Front Biosci. 2021; 13(1):30-43.

[29] Campillos M, Kuhn M, Gavin A-C, Jensen LJ, Bork P. Drug target identification using side-effect similarity. Science. 2008; 321(5886):263-66.

[30] Gallego V, Naveiro R, Roca C, Ríos Insua D, Campillo NE. AI in drug development: a multidisciplinary perspective. Mol Divers. 2021; 25(3):1461-79.

[31] Salo-Ahen OMH, Alanko I, Bhadane R, Bonvin AMJJ, Honorato RV, Hossain S, *et al*. Molecular dynamics simulations in drug discovery and pharmaceutical development. Processes. 2021; 9(1):71.

[32] Macalino SJY, Gosu V, Hong S, Choi S. Role of computer-aided drug design in modern drug discovery. Arch Pharm Res. 2015; 38(9):1686-701.

[33] Berman H, Henrick K, Nakamura H. Announcing the worldwide Protein Data Bank. Nat Struct Biol. 2003; 10(12): 980.

[34] Jiang Z, Zhou Y. Using bioinformatics for drug target identification from the genome. Am J Pharmacogenomics. 2005; 5(6):387-96.

[35] Farhadi T. Advances in protein tertiary structure prediction. Biomedical and biotechnology research journal. 2018; 2(1):20.

[36] Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, *et al*. SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic Acids Res. 2018; 46(W1):W296-w303.

[37] Webb B, Sali A. Comparative protein structure modeling using MODELLER. Curr Protoc Bioinformatics. 2016; 54:5.6.1-5.6.37.

[38] Yang J, Yan R, Roy A, Xu D, Poisson J, Zhang Y. The I-TASSER Suite: protein structure and function prediction. Nat Methods. 2015; 12(1):7-8.

[39] Moretti R, Lyskov S, Das R, Meiler J, Gray JJ. Web-accessible molecular modeling with Rosetta: The Rosetta Online Server that Includes Everyone (ROSIE). Protein Sci. 2018; 27(1):259-68.

[40] Bhattacharya D, Nowotny J, Cao R, Cheng J. 3Drefine: an interactive web server for efficient protein structure refinement. Nucleic Acids Res. 2016; 44(W1):W406-9.

[41] Krieger E, Joo K, Lee J, Lee J, Raman S, Thompson J, *et al*. Improving physical realism, stereochemistry, and side-chain accuracy in homology modeling: Four approaches that performed well in CASP8. Proteins. 2009; 77 Suppl 9(Suppl 9):114-22.

[42] Vyas VK, Ukawala RD, Ghate M, Chintha C. Homology modeling a fast tool for drug discovery: current perspectives. Indian J Pharm Sci. 2012; 74(1):1-17.

[43] Muhammed MT, Aki-Yalcin E. Homology modeling in drug discovery: Overview, current applications, and future perspectives. Chem Biol Drug Des. 2019; 93(1):12-20.

[44] Laskowski RA, MacArthur MW, Moss DS, Thornton JM. PROCHECK: a program to check the stereochemical quality of protein structures. J Appl Cryst. 1993; 26(2):283-91.

[45] Hooft RW, Vriend G, Sander C, Abola EE. Errors in protein structures. Nature. 1996; 381:272.

[46] Eisenberg D, Lüthy R, Bowie JU. VERIFY3D: assessment of protein models with three-dimensional profiles. Methods Enzymol. 1997; 277:396-404.

[47] Benkert P, Künzli M, Schwede T. QMEAN server for protein model quality estimation. Nucleic Acids Res. 2009; 37(suppl_2):W510-W4.

[48] Williams CJ, Headd JJ, Moriarty NW, Prisant MG, Videau LL, Deis LN, *et al*. MolProbity: More and better reference data for improved all-atom structure validation. Protein Sci. 2018; 27(1):293-315.

[49] Colovos C, Yeates TO. Verification of protein structures: patterns of nonbonded atomic interactions. Protein Sci. 1993; 2(9):1511-9.

[50] Bowie JU, Lüthy R, Eisenberg D. A method to identify protein sequences that fold into a known three-dimensional structure. Science. 1991; 253(5016):164-70.

[51] Pontius J, Richelle J, Wodak SJ. Deviations from standard atomic volumes as a quality measure for protein crystal structures. J Mol Biol. 1996; 264(1):121-36.

[52] Vemula D, Jayasurya P, Sushmitha V, Kumar YN, Bhandari V. CADD, AI and ML in drug discovery: A comprehensive review. Eur J Pharm Sci. 2023; 181:106324.

[53] Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, *et al*. UCSF Chimera--a visualization system for exploratory research and analysis. J Comput Chem. 2004; 25(13):1605-12.

[54] Biovia DS. Discovery Studio Visualizer. San Diego: Dassault Systèmes; 2017.

[55] Guex N, Peitsch MC. SWISS-MODEL and the Swiss-PdbViewer: an environment for comparative protein modeling. Electrophoresis. 1997; 18(15):2714-23.

[56] Laurie ATR, Jackson RM. Q-SiteFinder: an energy-based method for the prediction of protein–ligand binding sites. Bioinformatics. 2005; 21(9):1908-16.

[57] Wass MN, Kelley LA, Sternberg MJE. 3DLigandSite: predicting ligand-binding sites using similar structures. Nucleic Acids Res. 2010; 38(suppl_2):W469-W73.

[58] Huang B, Schroeder M. LIGSITE^{csc}: predicting ligand binding sites using the Connolly surface and degree of conservation. BMC Structural biology. 2006; 6(1):19.

[59] Brady GP, Stouten PFW. Fast prediction and visualization of protein binding pockets with PASS. J Comput Aided Mol Des. 2000; 14(4):383-401.

[60] Yang J, Roy A, Zhang Y. Protein–ligand binding site recognition using complementary binding-specific substructure comparison and sequence profile alignment. Bioinformatics. 2013; 29(20):2588-95.

[61] Jiménez J, Doerr S, Martínez-Rosell G, Rose AS, De Fabritiis G. DeepSite: protein-binding site predictor using 3D-convolutional neural networks. Bioinformatics. 2017; 33(19):3036-42.

[62] Chang Y, Hawkins BA, Du JJ, Groundwater PW, Hibbs DE, Lai F. A guide to *in silico* drug design. Pharmaceutics. 2023; 15(1):49.

[63] Halgren TA. Identifying and characterizing binding sites and assessing druggability. J Chem Inf Model. 2009; 49(2):377-89.

[64] Sheridan RP, Maiorov VN, Holloway MK, Cornell WD, Gao Y-D. Drug-like Density: A method of quantifying the "bindability" of a protein target based on a very large set of pockets and drug-like ligands from the protein data bank. J Chem Inf Model. 2010; 50(11):2029-40.

[65] Krasowski A, Muthas D, Sarkar A, Schmitt S, Brenk R. DrugPred: A Structure-based approach to predict protein druggability developed using an extensive non redundant data set. J Chem Inf Model. 2011; 51(11):2829-42.

[66] Volkamer A, Kuhn D, Rippmann F, Rarey M. DoGSiteScorer: a web server for automatic binding site prediction, analysis and druggability assessment. Bioinformatics. 2012; 28(15):2074-5.

[67] Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des. 2011; 7(2):146-57.

[68] Sharma A, Kunwar S, Vaishali, Agarwal V, Singh C, Sharma MD, *et al*. Molecular docking: an explanatory approach in structure-based drug designing and discovery. Int J Pharm Pharm Sci. 2021; 13(6):6-12.

[69] Grosdidier A, Zoete V, Michielin O. SwissDock, a protein-small molecule docking web service based on EADock DSS. Nucleic Acids Res. 2011; 39(Web Server issue):W270-7.

[70] Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, *et al*. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009; 30(16):2785-91.

[71] Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010; 31(2):455-61.

[72] van Zundert GCP, Rodrigues JPGLM, Trellet M, Schmitz C, Kastritis PL, Karaca E, *et al*. The HADDOCK2.2 Web Server: User-friendly integrative modeling of biomolecular complexes. J Mol Biol. 2016; 428(4):720-5.

[73] Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ. PatchDock and SymmDock: servers for rigid and symmetric docking. Nucleic Acids Res. 2005; 33(suppl_2):W363-W7.

[74] Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol. 2015; 1263:243-50.

[75] Kozakov D, Hall DR, Xia B, Porter KA, Padhorny D, Yueh C, *et al*. The ClusPro web server for protein-protein docking. Nat Protoc. 2017; 12(2):255-78.

[76] Baig MH, Ahmad K, Rabbani G, Danishuddin M, Choi I. Computer Aided Drug Design and its application to the development of potential drugs for neurodegenerative disorders. Curr Neuropharmacol. 2018; 16(6):740-8.

[77] Wang R, Lu Y, Wang S. Comparative evaluation of 11 scoring functions for molecular docking. J Med Chem. 2003; 46(12):2287-303.

[78] Li J, Fu A, Zhang L. An overview of scoring functions used for protein–ligand interactions in molecular docking. Interdiscip Sci. 2019; 11(2):320-8.

[79] Meng EC, Shoichet BK, Kuntz ID. Automated docking with grid-based energy evaluation. J Comput Chem. 1992; 13(4):505-24.

[80] Yin S, Biedermannova L, Vondrasek J, Dokholyan NV. MedusaScore: An accurate force field-based scoring function for virtual drug screening. J Chem Inf Model. 2008; 48(8):1656-62.

[81] Rastelli G, Rio AD, Degliesposti G, Sgobba M. Fast and accurate predictions of binding free energies using MM-PBSA and MM-GBSA. J Comput Chem. 2010; 31(4):797-810.

[82] Guedes IA, Barreto A, Marinho D, Krempser E, Kuenemann MA, Sperandio O, *et al*. New machine learning and physics-based scoring functions for drug discovery. Sci Rep. 2021; 11(1):1-19.

[83] Guedes IA, Pereira FSS, Dardenne LE. Empirical soring functions for structure-based virtual screening: applications, critical aspects, and challenges. Front Pharmacol. 2018; 10899.

[84] Böhm H-J. The development of a simple empirical scoring function to estimate the binding constant for a protein-ligand complex of known three-dimensional structure. J Comput Aided Mol Des. 1994;8(3):243-56.

[85] Eldridge MD, Murray CW, Auton TR, Paolini GV, Mee RP. Empirical scoring functions: I. The development of a fast empirical scoring function to estimate the binding affinity of ligands in receptor complexes. J Comput Aided Mol Des. 1997; 11(5):425-45.

[86] Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, *et al*. Glide: A new approach for rapid, accurate docking and scoring. 1. method and assessment of docking accuracy. J Med Chem. 2004; 47(7):1739-49.

[87] Li G-B, Yang L-L, Wang W-J, Li L-L, Yang S-Y. ID-Score: A New empirical scoring function based on a comprehensive set of descriptors related to protein–ligand interactions. J Chem Inf Model. 2013; 53(3):592-600.

[88] Yang C, Zhang Y. Lin_F9: A linear empirical scoring function for protein–ligand docking. J Chem Inf Model. 2021; 61(9):4630-44.

[89] Muegge I. A knowledge-based scoring function for protein-ligand interactions: Probing the reference state. Perspectives in drug discovery and design. 2000; 20(1):99-114.

[90] Velec HF, Gohlke H, Klebe G. DrugScore CSD knowledge-based scoring function derived from small molecule crystal data with superior recognition rate of near-native ligand poses and better affinity prediction. J Med Chem. 2005; 48(20):6296-303.

[91] Muegge I. PMF scoring revisited. J Med Chem. 2006; 49(20):5895-902.

[92] Wang X, Zhang D, Huang S-Y. New knowledge-based scoring function with inclusion of backbone conformational entropies from protein structures. J Chem Inf Model. 2018; 58(3):724-32.

[93] Feng Y, Huang S-Y. ITScore-NL: An iterative knowledge-based scoring function for nucleic acid–ligand interactions. J Chem Inf Model. 2020; 60(12):6698-708.

[94] Betzi S, Suhre K, Chétrit B, Guerlesquin F, Morelli X. GFscore: A general nonlinear consensus scoring function for high-throughput docking. J Chem Inf Model. 2006; 46(4):1704-12.

[95] Bar-Haim S, Aharon A, Ben-Moshe T, Marantz Y, Senderowitz H. SeleX-CS: A new consensus scoring algorithm for hit discovery and lead optimization. J Chem Inf Model. 2009; 49(3):623-33.

[96] Zheng Z, Merz KM Jr. Development of the knowledge-based and empirical combined scoring algorithm (KECSA) to score protein–ligand interactions. J Chem Inf Model. 2013; 53(5):1073-83.

[97] Debroise T, Shakhnovich EI, Chéron N. A hybrid knowledge-based and empirical scoring function for protein–ligand interaction: SMoG2016. J Chem Inf Model. 2017; 57(3):584-93.

[98] Van Der Spoel D, Lindahl E, Hess B, Groenhof G, Mark AE, Berendsen HJ. GROMACS: fast, flexible, and free. J Comput Chem. 2005; 26(16):1701-18.

[99] Case DA, Cheatham TE 3rd, Darden T, Gohlke H, Luo R, Merz KM Jr, *et al*. The Amber biomolecular simulation programs. J Comput Chem. 2005; 26(16):1668-88.

[100] Christen M, Hünenberger PH, Bakowies D, Baron R, Bürgi R, Geerke DP, *et al*. The GROMOS software for biomolecular simulation: GROMOS05. J Comput Chem. 2005; 26(16):1719-51.

[101] Phillips JC, Braun R, Wang W, Gumbart J, Tajkhorshid E, Villa E, *et al*. Scalable molecular dynamics with NAMD. J Comput Chem. 2005; 26(16):1781-802.

[102] Brooks BR, Brooks 3rdCL, Mackerell Jr. AD, Nilsson L, Petrella RJ, Roux B, *et al*. CHARMM: the biomolecular simulation program. J Comput Chem. 2009; 30(10):1545-614.

[103] Katsila T, Spyroulias GA, Patrinos GP, Matsoukas M-T. Computational approaches in target identification and drug discovery. Comput Struct Biotechnol J. 2016; 14:177-84.

[104] Shim J, Mackerell AD Jr. Computational ligand-based rational design: Role of conformational sampling and force fields in model development. Med Chem Comm. 2011; 2(5):356-70.

[105] Yu W, MacKerell AD Jr. Computer-aided drug design methods. Methods Mol Biol. 2017; 1520:85-106.

[106] Keiser MJ, Roth BL, Armbruster BN, Ernsberger P, Irwin JJ, Shoichet BK. Relating protein pharmacology by ligand chemistry. Nat Biotechnol. 2007; 25(2):197-206.

[107] Zoete V, Daina A, Bovigny C, Michielin O. Swiss Similarity: A web tool for low to ultra-high throughput ligand-based virtual screening. J Chem Inf Model. 2016; 56(8):1399-1404.

[108] Seidel T, Wieder O, Garon A, Langer T. Applications of the pharmacophore concept in natural product inspired drug design. Mol Inform. 2020; 39(11):2000059.

[109] Kaserer T, Beck KR, Akram M, Odermatt A, Schuster D. Pharmacophore models and pharmacophore-based virtual screening: concepts and applications exemplified on hydroxysteroid dehydrogenases. Molecules. 2015; 20(12):22799-832.

[110] Chen J, Lai L. Pocket v. 2: further developments on receptor-based pharmacophore modeling. J Chem Inf Model. 2006; 46(6):2684-91.

[111] Schneidman-Duhovny D, Dror O, Inbar Y, Nussinov R, Wolfson HJ. PharmaGist: a webserver for ligand-based pharmacophore detection. Nucleic Acids Res. 2008; 36(suppl_2): W223-W8.

[112] Wolber G, Langer T. LigandScout: 3-D Pharmacophores derived from protein-bound ligands and their use as virtual screening filters. J Chem Inf Model. 2005; 45(1):160-9.

[113] Koes DR, Camacho CJ. ZINCPharmer: pharmacophore search of the ZINC database. Nucleic Acids Res. 2012; 40(W1):W409-W14.

[114] Prajapat D, Gupta S, Talesara G. Significance of computer aided drug design and 3D QSAR in modern drug discovery. J Med Org Chem. 2017; 1:1-2.

[115] Zhang Y, Luo M, Wu P, Wu S, Lee T-Y, Bai C. Application of computational biology and artificial intelligence in drug design. Int J Mol Sci. 2022; 23(21):13568.

[116] Rudrapal M, Chetia DD. Virtual Screening, Molecular Docking and QSAR Studies in Drug Discovery and Development Programme. Journal of Drug Delivery and Therapeutics. 2020; 10:225-33.

[117] Du H, Hu Z, Bazzoli A, Zhang Y. Prediction of inhibitory activity of epidermal growth factor receptor inhibitors using grid search-projection pursuit regression method. PloS one. 2011; 6:e22367.

[118] Verma J, Khedkar V, Coutinho E. 3D-QSAR in drug design–a review. Curr Top Med Chem. 2009; 10:95-115.

[119] Sen D, Farooqui NA, Easwari TS, Roy B. CoMFA-3D QSAR approch in drug design. International Journal of Research and Development in Pharmacy and Life Sciences. 2012; 1:167-75.

[120] Halder A, Amin SA, Jha T, Gayen S. Insight into the structural requirements of pyrimidine-based phosphodiesterase 10A (PDE10A) inhibitors by multiple validated 3D QSAR approaches. SAR QSAR Environ Res. 2017; 28:1-21.

[121] Srivastava V, Kumar A, Mishra B, Siddiqi M. CoMFA and CoMSIA 3D-QSAR analysis of DMDP derivatives as anti-cancer agents. Bioinformation. 2008; 2:384-91.

[122] Dong J, Yao ZJ, Zhu MF, *et al*. ChemSAR: an online pipelining platform for molecular SAR modeling. J Cheminform. 2017; 9(1):27.

[123] Ragno R. www.3d-qsar.com: a web portal that brings 3-D QSAR to all electronic devices-the Py-CoMFA web application as tool to build models from pre-aligned datasets. J Comput Aided Mol Des. 2019; 33(9):855-864.

[124] Wang YL, Wang F, Shi XX, *et al*. Cloud 3D-QSAR: a web tool for the development of quantitative structure-activity relationship models in drug discovery. Brief Bioinform. 2021; 22(4):bbaa276.

[125] Lima AN, Philot EA, Trossini GHG, Scott LPB, Maltarollo VG, Honorio KM. Use of machine learning approaches for novel drug discovery. Expert Opin Drug Discov. 2016; 11(3):225-39.

[126] Maia EHB, Assis LC, de Oliveira TA, da Silva AM, Taranto AG. Structure-based virtual screening: from classical to artificial intelligence. Front Chem. 2020; 8:343.

[127] Lin Y. Review of modern computer-aided drug design methods. International Journal of Biology and Life Sciences. 2022; 1:47-50.

[128] Berman HM, Kleywegt GJ, Nakamura H, Markley JL. The future of the Protein Data Bank. Biopolymers. 2013; 99(3):218-22.

[129] Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, *et al*. PubChem substance and compound databases. Nucleic Acids Res. 2016; 44(D1):D1202-13.

[130] Bento AP, Gaulton A, Hersey A, Bellis LJ, Chambers J, Davies M, *et al*. The ChEMBL bioactivity database: an update. Nucleic Acids Res. 2014; 42(D1):D1083-D90.

[131] Pence HE, Williams A. ChemSpider: An online chemical information resource. J. Chem. Educ. 2010; 87(11):1123-4.

[132] Sterling T, Irwin JJ. ZINC 15–ligand discovery for everyone. J Chem Inf Model. 2015; 55(11):2324-37.

[133] Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, *et al*. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2018; 46(D1):D1074-D82.

[134] Zeng X, Zhang P, He W, Qin C, Chen S, Tao L, *et al*. NPASS: natural product activity and species source database for natural product research, discovery and tool development. Nucleic Acids Res. 2018; 46(D1):D1217-d22.

[135] Wilson GL, Lill MA. Integrating structure-based and ligand-based approaches for computational drug design. Future Med Chem. 2011; 3(6):735-50.

[136] Drwal MN, Griffith R. Combination of ligand-and structure-based methods in virtual screening. Drug Discov Today Technol. 2013; 10(3):e395-e401.

[137] Leelananda SP, Lindert S. Computational methods in drug discovery. Beilstein J Org Chem. 2016; 12:2694-718.

[138] Muegge I, Oloff S. Advances in virtual screening. Beilstein J Org Chem. 2006; 3(4):405-11.

[139] Vázquez J, López M, Gibert E, Herrero E, Luque FJ. Merging ligand-based and structure-based methods in drug discovery: An overview of combined virtual screening approaches. Molecules. 2020; 25(20):4723.

[140] Daina A, Zoete V. Application of the SwissDrugDesign online resources in virtual screening. Int J Mol Sci. 2019; 20(18):4612.

[141] Ursu O, Rayan A, Goldblum A, Oprea TI. Understanding drug-likeness. WIREs Comp Mol Sci. 2011;1(5):760-81.

[142] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 1997;23(1):3-25.

[143] Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Comb Chem. 1999; 1(1):55-68.

[144] Muegge I, Heald SL, Brittelli D. Simple selection criteria for drug-like chemical matter. J Med Chem. 2001; 44(12):1841-6.

[145] Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002; 45(12):2615-23.

[146] Caldwell GW, Yan Z, Tang W, Dasgupta M, Hasting B. ADME optimization and toxicity assessment in early- and late-phase drug discovery. Curr Top Med Chem. 2009; 9(11):965-80.

[147] Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? Acta Pharm Sin B. 2022; 12(7):3049-62.

[148] Cao D, Wang J, Zhou R, Li Y, Yu H, Hou T. ADMET evaluation in drug discovery. 11. PharmacoKinetics Knowledge Base (PKKB): a comprehensive database of pharmacokinetic and toxic properties for drugs. J Chem Inf Model. 2012; 52(5):1132-7.

[149] Lee IH, Kim HJ, Chang GS, Chung JE, No KT. The PreADME Approach: Web-based program for rapid prediction of physico-chemical, drug absorption and drug-like properties. In: EuroQSAR 2002, ed. Designing drugs and crop protectants: processes, problems and solutions. 2003. p. 418-420.

[150] Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017; 7:42717.

[151] Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem. 2015; 58(9):4066-4072.

[152] Yang H, Lou C, Sun L, *et al*. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Bioinformatics. 2019; 35(6):1067-1069.

[153] Mousavi S, Zare S, Mirzaei M, Feizi A. Novel drug design for treatment of COVID-19: A systematic review of preclinical studies. Can J Infect Dis Med Microbiol. 2022; 2022:2044282.

[154] Alrasheid AA, Babiker MY, Awad TA. Evaluation of certain medicinal plants compounds as new potential inhibitors of novel corona virus (COVID-19) using molecular docking analysis. In Silico Pharmacol. 2021; 9(1):10.

[155] Enmozhi SK, Raja K, Sebastine I, Joseph J. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. J Biomol Struct Dyn. 2021; 39(9):3092-8.

[156] Arwansyah A, Arif AR, Ramli I, Kurniawan I, Sukarti S, Nur Alam M, *et al*. Molecular modelling on SARS-CoV-2 papain-like protease: an integrated study with homology modelling, molecular docking, and molecular dynamics simulations. SAR QSAR Environ Res. 2021; 32(9):699-718.

[157] Kumar BK, Faheem, Sekhar KVGC, Ojha R, Prajapati VK, Pai A, *et al*. Pharmacophore based virtual screening, molecular docking, molecular dynamics and MM-GBSA approach for identification of prospective SARS-CoV-2 inhibitor from natural product databases. J Biomol Struct Dyn. 2022; 40(3):1363-86.

[158] Idris MO, Yekeen AA, Alakanse OS, Durojaye OA. Computer-aided screening for potential TMPRSS2 inhibitors: a combination of pharmacophore modeling, molecular docking and molecular dynamics simulation approaches. J Biomol Struct Dyn. 2021; 39(15):5638-56.

[159] Zarezade V, Rezaei H, Shakerinezhad G, Safavi A, Nazeri Z, Veisi A, *et al*. The identification of novel inhibitors of human angiotensin-converting enzyme 2 and main protease of Sars-Cov-2: A combination of in silico methods for treatment of COVID-19. J Mol Struct. 2021; 1237:130409.

[160] Ferraz WR, Gomes RA, S Novaes AL, Goulart Trossini GH. Ligand and structure-based virtual screening applied to the SARS-CoV-2 main protease: an *in silico* repurposing study. Future Med Chem. 2020; 12(20):1815-1828.

[161] Gil C, Ginex T, Maestro I, *et al*. COVID-19: Drug targets and potential treatments. J Med Chem. 2020; 63(21):12359-12386.

[162] Gupta Y, Savytskyi OV, Coban M, Venugopal A, Pleqi V, Weber CA, *et al*. Protein structure-based in-silico approaches to drug discovery: Guide to COVID-19 therapeutics. Mol Aspects Med. 2023; 91:101151.

[163] Padmanabhan P, Desikan R, Dixit NM. Targeting TMPRSS2 and Cathepsin B/L together may be synergistic against SARS-CoV-2 infection. PLoS Comput Biol. 2020; 16(12):e1008461.

[164] Jamiu AT, Pohl CH, Bello S, Adedoja T, Sabiu S. A review on molecular docking analysis of phytocompounds against SARS-CoV-2 druggable targets. All Life. 2021; 14(1):1100-28.

[165] Rani I, Kalsi A, Kaur G, Sharma P, Gupta S, Gautam RK, *et al*. Modern drug discovery applications for the identification of novel candidates for COVID-19 infections. Ann Med Surg. 2022; 80:104125.