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Approaches for Drug Design and Discovery

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Abstract

Drug discovery in general requires high costs and especially a very long time, which is around 11-16 years. This is because drug development must go through a complete series of research processes to obtain comprehensive data. However, in line with the community's need for the availability of quality drugs, having good efficacy and safety, the development of drug development technology using a computing system is carried out. This is in line with the development of science and collaboration between various disciplines. Approaches that can be used for computational drug discovery include Structure-Based Drug Design and Ligand Based Drug Design which are proven to accelerate and increase the possibility of finding new drugs. This article aims to provide an overview of several approaches to drug discovery development, especially the benefits of computational. The data were collected from 28 primary published journals and 28 supporting literatures. This article discusses the two computational methods, especially from the application aspect which is expected to be useful in the field of drug discovery and development to be more efficient in terms of time and cost. The traditional approach to new drug development takes about 11-16 years but using computational methods can shorten the drug discovery stage to 9-13 years.

Keywords: Drug Discovery, Ligand Based CADD, Structure-Based CADD

1. Introduction

The pharmaceutical industry and educational institutions consistently find and develop drugs for various diseases according to the needs of the community in improving their health. Drug discovery efforts have been started since 450 M when people have used plants and animals that are thought to have certain compounds that are efficacious in healing. At 2.5 M – 0.2M, humans have discovered the medicinal properties of natural products such as plants and animals. 5000 years ago, medical personnel were first recorded in Egyptian papyrus scrolls using natural products for treatment. In 1652, Nicholas Culpepper's Herbs was published. Then in 1800, synthetic organic chemical origins were

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identified such as quinine, aspirin, and heroin. Furthermore, in 1900-1950, insulin, penicillin, and streptomycin were discovered. Continued in 1960-1970, discovered hormone receptors and recombinant DNA methods. In 1980, the first targeted drug discovery and high-throughput screening were carried out. The discovery continued until 1990, there was a human genome project and in the 21st century, target-directed drug discovery is still often the method of choice for drug discovery [1]. This effort continues and traditionally drug discovery will go through a series of processes starting from the drug discovery stage which takes between 3-5 years with research on extraction and collection of compounds, target identification, target validation, development of compound assays, and determination of potential compounds or compounds. known as lead compounds. The next stage is pre-clinical which takes 1-2 years. At this stage the 250 selected compounds will be further tested in terms of in vitro and in vivo toxicity, the determination of ADMET to determination of pharmacokinetics/pharmacodynamics or known as PK/PD. The next stage is the clinical trial phase which consists of phase I, phase II, and phase III clinical trials of 5 potential compounds which usually takes about 6-7 years. In the final stage, when a new drug compound has been determined, product registration will be carried out to obtain a distribution permit to be marketed. After being marketed, monitoring and evaluation of drugs are still carried out which is known as pharmacovigilance testing [2,3].

Efforts to find these drugs will generally take 11-16 years or even more than that. This is felt to be inefficient in terms of cost and time, whereas currently the medicines in question are very much needed by the community. With the development of science, a computational system for drug discovery was developed called SBDD and LBDD. This system combines the results of research that has been carried out on validated protein targets and existing drugs, then attempts to use that information to obtain compounds that are suitable for specific disease protein targets. These advances have reduced the time required for the initial drug screening period and hit to lead screening, so that time and cost efficiencies in drug discovery can be achieved [4].

2. Method

The method used in this article review is to search the internet through Google Scholar and the NCBI website (the selected category is PubMed) with the keywords "drug discovery process" drug discovery and structure-based discovery" "ligand-based drug discovery". The sources used as references are national and international journals and articles that discuss keywords. The exclusion criteria are articles that are not in accordance with the topic of discussion, published more than 20 years, and lack of detailed information about drug discovery and development. The data were collected from 28 primary published journals and 28 supporting literatures.

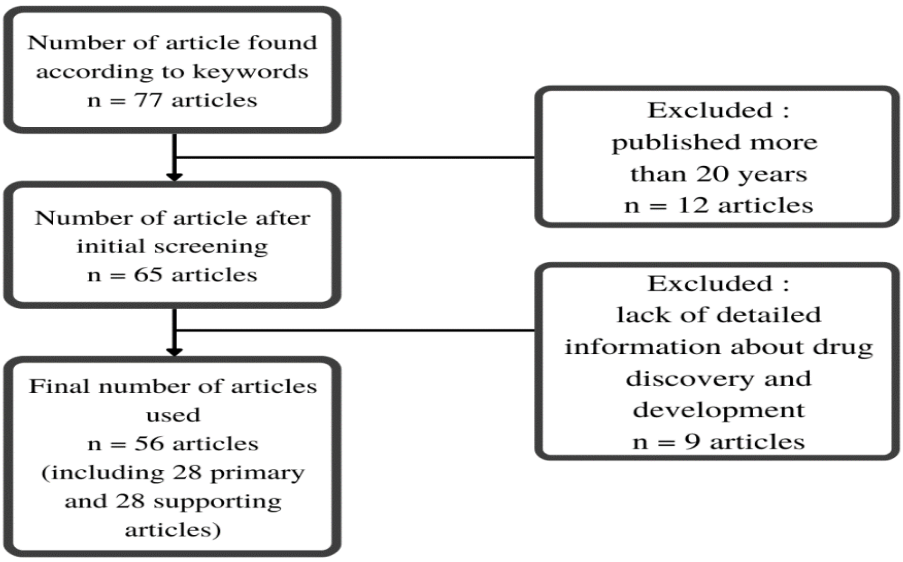

Figure 1. Flow Chart or Selection of Articles

3. Discussion

3.1 Drug Discovery

Drug discovery is the process of identifying a molecule as a potential drug candidate. The aim of this is to obtain one or more candidate molecules that have biological activity on a target that is relevant to disease and safe for use/testing on humans as drugs. It takes more than one drug candidate compound because not all compounds can meet the test criteria which are usually due to safety, kinetics, potency, and other factors. Drug discovery differs from drug development which is a drug development process carried out with preclinical and clinical testing stages to evaluate the activity and safety of a compound in which a compound molecule must have pharmacokinetic properties that allow a consistent relationship between the drug dose given, exposure, and binding drug at the desired therapeutic target. The purpose of this drug development is to get FDA approval so that the drug can be marketed [5,6].

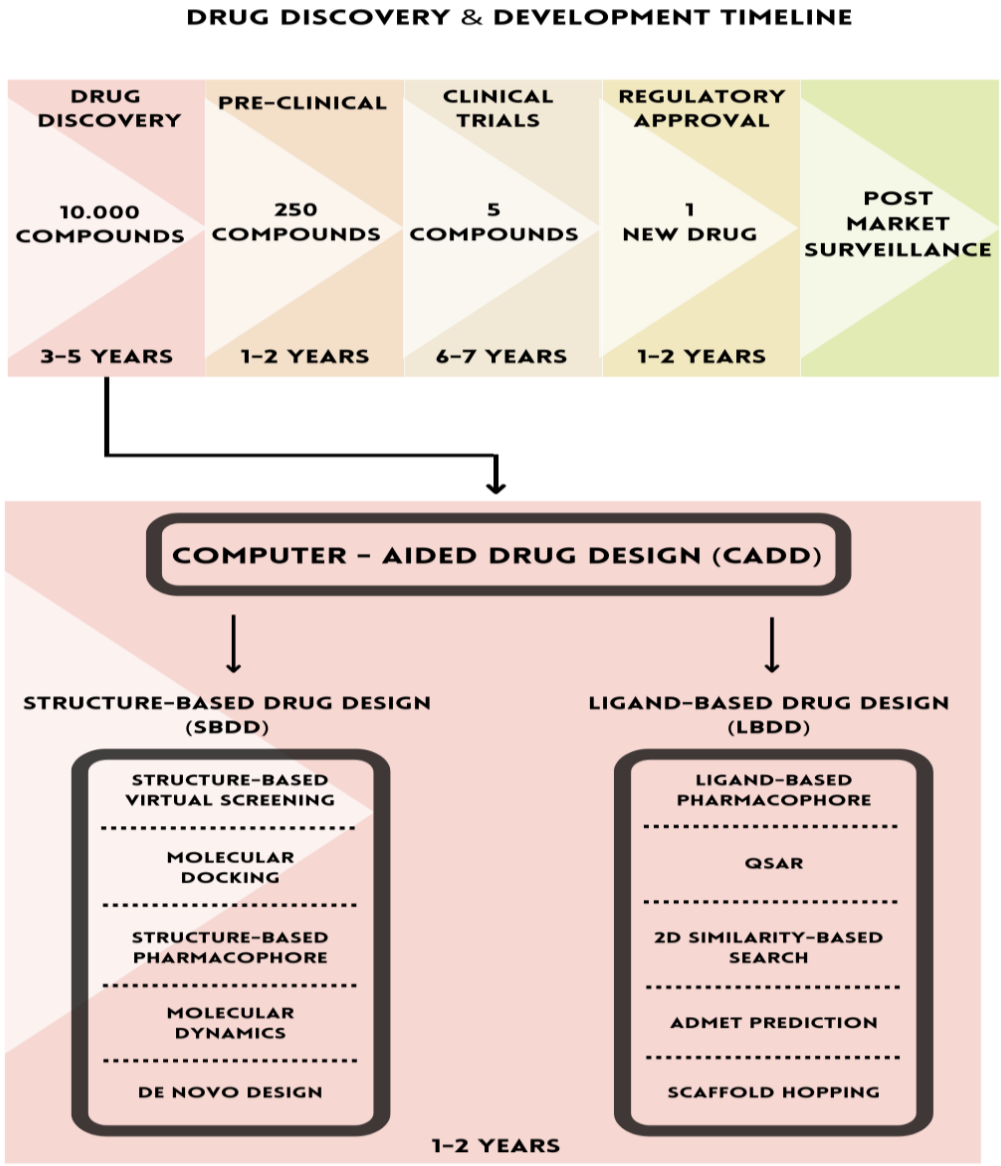

Figure 2. Drug Discovery & Development Timeline

The drug discovery process is a challenge for the pharmaceutical industry due to the time-consuming and high-cost process. In general, the research and development process take about 3-5 years, preclinical testing takes about 1-2 years, clinical trials take about 6-7 years and the review and approval process takes about 1-2 years as shown in **Figure 2**.

Initial processes in the early stages of drug discovery are target identification, target validation, hit and lead identification, and lead optimization.

a. Target Identification

The first step in drug discovery is to identify potential drug targets and their role in treating a disease. A target is generally a single molecule, such as a gene or protein involved in a particular disease. Identification of the target begins with isolating the function of the possible therapeutic target and characterizing the molecule.

Targets that are considered ideal are targets that are efficacious, safe, and meet clinical and commercial requirements. The methods used for target identification can be based on the principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines [7,8,9]. Approaches used to target identification include phenotypic screening, genetic approaches such as expression cloning techniques, in silico or chemical proteomic-based approaches, and genetic association studies [10,11].

b. Target Validation

Once a drug target has been identified, a rigorous evaluation needs to be carried out to demonstrate that the target will have the desired therapeutic effect. In the drug discovery process, the main obstacle is at this stage [12]. In general, target validation is carried out by genetic manipulation of the target gene (in vitro) which involves knocking down genes (shRNA, siRNA, miRNA), knocking out genes (CRISPR), and knocking genes (transfection of viruses from mutant genes) using antibodies that will interact with the target with high affinity and block further interactions and using genomic chemistry which is a chemical approach to genome-coding proteins [13].

c. Hit and Lead Identification

In drug discovery, the identification of the 'hit' molecule is the starting point for the hit-to-lead process. The ‘hit-to-lead’ phase is usually a follow-up to high-throughput (HTS) screening. A 'hit' molecule can be identified by one or more of several technology-based approaches such as high throughput biochemical and cellular assays, natural product testing, structure-based design, peptides and peptidomimetics, chemogenomics, virtual bycatch, and literature and patent-based innovations [14]. The 'lead' compound requires structural activity relationships as well as the determination of synthetic feasibility and preliminary evidence of in vivo activity and target involvement. To reduce the number of compounds that fail in the drug development process, drug performance assessments are often carried out. This assessment is important to do to convert 'lead' compounds into drugs. For a compound to be considered a drug, a compound must have the potential to bind to a specific target and have a good pharmacokinetic profile [15].

d. Lead Optimization

Optimization of 'lead' compounds is a process to improve the chemical structure of a drug candidate after the initial lead compound has been identified to improve its characteristics as a drug candidate. This process involves a series of iterative syntheses and characterizations of potential drugs to build a representation of how chemical structure and activity relate in terms of interactions with targets and their metabolism. Lead compounds were evaluated by various aspects, including selectivity and binding mechanism during the optimization of lead compounds. The purpose of this optimization is to maintain the beneficial properties while at the same

time correcting deficiencies in the structure of the 'lead' compound. In addition, it is necessary to evaluate the pharmacokinetic parameters, pharmacodynamics, and toxicological properties [16].

3.2 Preclinical Test

Preclinical testing is a drug development process that evaluates the safety and efficacy of drugs in animal species to conclude prospective results in humans. To carry out this test, approval from the relevant regulatory authority is required. Where regulatory authorities must ensure that trials are carried out safely and ethically and are only carried out for drugs that are confirmed to be safe and effective. Preclinical testing can be done in two ways, namely general pharmacology and toxicology. Pharmacology is concerned with the pharmacokinetic and pharmacodynamic parameters of drugs. Toxicological studies of drugs can be carried out by in-vitro and in-vivo assays [17,18].

3.3 Clinical Trials

Clinical trials are tests on human volunteers to answer questions about the safety and efficacy of a new drug or method. Clinical trials follow a specific study protocol designed by the researcher or manufacturer. During clinical trials, researchers need to select patients with predetermined characteristics, determine the number of participants who take part in the study, duration of testing, administer treatment (dose and dosage form administration), make parameter assessments, and collect patient health data for some time specific for later analysis. The clinical trial consisted of 3 testing phases where phase 1 was carried out on 20-80 volunteers to evaluate safety and dosage, phase 2 was carried out on 100-300 volunteers to evaluate efficacy and side effects, and phase 3 was conducted on 300-3000 volunteers to the monitoring of efficacy and adverse drug reactions [9,19].

3.4 Product Registration to Get Marketing Permit from the Food and Drug Supervisory Agency

The New Drug Application (NDA) aims to verify that a drug is safe and effective for use in the person being studied. It is necessary to include everything about the drug from preclinical data to phase 3 clinical trial data in the NDA. In addition, it is necessary to include labeling, security updates, patent information, and instructions for use. Once complete data is obtained for an NDA, it will take the FDA approximately 6-10 months to decide to approve an NDA. If the FDA has declared that a drug is safe and effective for use, then the developer needs to increase the information about the drug by labeling it. Proper labeling determines the basis for approval and direction for drug use. Developers can choose to continue further development or not and if the developer objected to the FDA's decision, an appeal could be made [20,21].

3.5 Approach Method with Computing

The computational approach method is a computer-aided drug design technique and is usually used for drug discovery such as Structure-Based Drug Design and Ligand Based Drug Design. Where structure-based drug design consists of structure-based virtual screening, molecular docking, de novo drug design, molecular dynamics, and pharmacophore modeling. Meanwhile, ligand-based drug design consists of QSAR, pharmacophore

modeling, and ligand-based virtual screening.

3.5.1 Structure-Based Drug Design

Structure-Based Drug Design (SBDD) is a more specific, efficient, and fast approach to leading compound discovery and optimization. SBDD refers to the systematic use of structured data such as target macromolecules (receptors) which are usually obtained experimentally or through computational modeling. The aim is to understand and design ligands in such a way that they have high receptor binding affinity. Drug targets are generally key molecules involved in the metabolism or cell signaling pathways of certain cells that are known to have activity in certain diseases [14]. Current SBDD methods allow the design of ligands containing the features required for efficient modulation of target receptors [22,23]. Selective modulation of drug targets validated by high-affinity ligands interferes with certain cellular processes which in turn leads to the desired pharmacological and therapeutic effects [24].

SBDD uses the geometric shape/3D structure of the target protein sourced from the Protein Data Bank (GDP) and understands disease at the molecular level [25]. SBDD begins with knowing the structure of the target, then an *in silico* study is conducted to identify potential ligands followed by an evaluation of biological properties, such as potency, affinity, efficacy, and ADMET properties of a compound [26,27]. Molecular docking, structure-based virtual screening, and molecular dynamics are one of the most frequently used SBDD strategies due to their wide application in the analysis of a molecule such as binding energy, molecular interactions, and evaluation of conformational changes that occur during the docking process [28].

The software needed in SBDD includes AutoDock Vina to combine protein structure data obtained from PDB with ligand data. However, if the protein in question is not available, it can be made using the homology modeling method using the MODELLER or SWISS-MODEL program. Other software that is also needed is Discovery Studio, OpenEye, Schrödinger, and MOE.

a. Structure-Based Virtual Screening

The SBVS method relies on the structure of the target protein's active site which in the SBVS database the compound will be anchored to the target binding site [29, 25]. Along with the prediction of the binding mode, SBVS provides a rating of the tethered molecule which will be used as the sole criterion for selecting a potential molecule or can be combined with other evaluation methods. The selected compounds were then experimentally evaluated to determine their biological activity on the molecular targets under investigation [30].

Broadly speaking, the steps for SBVS are preparation of molecular targets, selection of compound database, molecular anchoring, and post-docking analysis [31]. The conformational change resulting from the interaction with the ligand is an important matter that requires consideration in selecting the appropriate structure. The selected structure needs to be prepared to carry out the docking procedure properly by adding hydrogen atoms, removing water molecules, determining the correct protonation and

tautomerization status of the binding site residues, and calculating partial charges [32]. Next, the prepared database is installed at the target binding site. A potential ligand is when the energy of each molecule has a high score. Post docking analysis is usually carried out to decide which compound will be the lead compound [33].

b. Molecular Docking

Docking is a molecular interaction simulation technique. Molecular docking predicts conformational and ligand binding in the target active site with high accuracy and is the most frequently used technique in SBDD [34,35]. This method is applied to study molecular phenomena such as ligand binding and intermolecular interactions for the stability of a complex [36]. In addition, the docking algorithm predicts the binding energy and the ranking of the ligands through various assessments. There are two types of molecular docking, namely flexible-ligand search docking and flexible-protein docking [37].

c. Structure-Based Pharmacophore

The pharmacophore model of the target binding site encapsulates the steric and electronic requirements for optimal ligand-target interactions. The most common properties used to define a pharmacophore are hydrogen bond acceptor, hydrogen bond donor, basic group, acid group, partial charge, aliphatic hydrophobic group, and aromatic hydrophobic group. Besides being able to be used for virtual compound screening, pharmacophore models can be used by de novo design algorithms to guide the design of new compounds. Structure-based pharmacophore methods were developed based on the analysis of target binding sites or based on the structure of the target ligand complex [38,39].

d. Molecular Dynamics

The flexibility of the target binding site is an important aspect that is often overlooked in the consideration of molecular docking. Enzymes and receptors can undergo conformational changes during the molecule recognition process. In some cases these structural rearrangements are minor and the ligands fit at the binding site with little mobility or significant conformational changes in some proteins that may involve secondary and tertiary structural elements. This flexibility-related problem can be addressed using molecular dynamics techniques [40,41]. MD simulations can generate alternative conformational states corresponding to the ligand-induced structure. In the absence of a suitable crystallographic structure for the molecular target, MD can be applied to produce a good set of structures for docking [42]. MD can also be used to estimate the stability of the ligand-receptor complex proposed by molecular docking [43]. MD has the drawbacks of high computational costs for simulating large systems usually consisting of thousands of atoms when the ligand-receptor complex is being studied and the conformational changes that the receptor undergoes during molecular recognition exceed the available computational timescale capacities [44]. However, MD makes an important contribution to SBDD,

especially when combined with other methods such as molecular docking.

e. De Novo Design

De novo drug design is a method of forming new chemical compounds starting from molecular units. The essence of this approach is to develop a chemical structure of a small molecule that binds to a target with good affinity [45]. Two methods can be used, namely ligand-based de novo and receptor-based de novo. The quality of the target protein structure and knowledge of the binding site are important to know if you want to use a receptor-based design because suitable small molecules are designed to incorporate fragments into the binding of the receptor. This can be done by crystallizing the ligand with the receptor [46]. The greatest challenge in the design of this de novo drug cannot be separated from its greatest advantages. By defining compounds that have never been seen before, it is necessary to attempt synthesis for acquisition before testing. This affected the de novo protocol where it was necessary to incorporate synthesis capability metrics into the assessment. This will increase the effort required such as costs, results, time, and also the required expertise. Thus, synthesizing capability becomes increasingly important when designing large numbers of compounds [47].

3.5.2 Ligand-Based Based Drug Design

Ligand Based Drug Design (LBDD) is an approach if in some cases data relating to the 3D structure of a target protein are not available, then drug design can be based on a process that uses known ligands of the target protein as a starting point. QSAR and pharmacophore modeling are methods that are often used in the drug design process using the LBDD approach [48]. Using fingerprints of known ligand molecules, databases can be screened for similar molecular fingerprints [49]. The general structural features of the ligands can be found by pharmacophore modeling which can then be used for molecular screening [50]. To predict the activity of new molecules, models can be built with QSAR. While pharmacophore modeling only shows the activity of the active ligand, the relationship between the chemical/physical properties of the ligand and biological activity can be explored more fully using the QSAR model [51]. The software needed for LBDD includes AutoDock Vina, Schrödinger, LiSiCA, BioSolveIT, and many others. Consisting of 5 methods that can be done are QSAR, Ligand-Based Pharmacophore, 2D Similarity-Based Search, ADMET Prediction, and Scaffold Hopping. However, 3 of them that are commonly used are QSAR, Ligand-Based Pharmacophore, and 2D Similarity-Based Search.

a. Ligand-Based Pharmacophore

Among the ligand-based virtual screening techniques, the pharmacophore modeling approach is one of the best. This approach requires the introduction of a 3D pharmacophore preparation using a list of known active substances that should bind to the same active site or from the 3D coordinates of the protein active site. The advantage of using a pharmacophore is that it can be computationally visualized, superimposed onto a list of molecules,

and thus assist medicinal chemists in synthesizing new molecules [52,53].

b. QSAR
QSAR describes the mathematical relationship between structural attributes and target response. The flow of drug discovery based on QSAR is started by collecting a group of active and inactive ligands, then creating a mathematical descriptor that describes the physicochemical and structural properties of a compound. A model was created to identify the relationship between descriptors and experimental activity and maximize predictive power. Finally, a model was applied to predict the activity of the test compound encoded with the same descriptor. The success of QSAR depends not only on the initial quality of the compound but also on the choice of the descriptor and the ability to generate suitable mathematical relationships. One of the important considerations regarding this method is the fact that all the resulting models will depend on the sampling space of compounds with known activity [54].

c. 2D Similarity-Based Search
Goldman and Wipke presented a new approach to shape-based molecular similarity search [55]. This method is capable of locating different molecules by using a geometrically invariant molecular surface descriptor. This method uses a superimposition algorithm that uses this geometric invariance to recognize similar regions of the surface shape that exist in two molecules [56]. The calculation of the shape descriptor continues by considering initially all the conformations of the molecule to define the shape descriptor space; the chemical features in each feature lattice shape and location are then co-coded into a bit binary string descriptor. Identification of the most important bits for the activity leads to a model that can judge the library on the number of bits the ensemble matches.

4. Conclusion

Several approaches including the traditional drug discovery process and modern computational approach are useful in finding novel drugs. Nevertheless, Structure-Based Drug Design and Ligand-Based Drug Design approaches that are computationally based are currently known as preferable alternatives in drug discovery because they are more efficient in terms of time and cost. This is considered very important since alternative drugs with several beneficial effects or alternatives to existing drugs are urgently required for the enhancement of human health. The traditional approach to new drug development takes about 11-16 years but using computational methods can shorten the drug discovery stage to 9-13 years.

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