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REVIEW ARTICLE

Computational Chemistry: A game-changer in the drug discovery field

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ABSTRACT

The greater development in the computational tools and the presence of a huge number of established chemical libraries emerge the inquiry about the ability to integrate the computational techniques in the drug discovery process. This review emphasizes the role of computational tools and software to accelerate the steps in the drug discovery pipeline. The data were gathered from the trendiest research articles and reviews that were indexed in the well-established scholarly search engines. Different vital techniques, such as virtual screening, pharmacophore modeling, molecular docking, molecular dynamic simulations, and quantitative structure activity relationship, are widely employed for target recognition, lead refining, and forecasting binding behavior at the atomic level. The advancement in artificial cognitive computing software significantly expanded the capabilities for rapid analysis of substantial data sets and the generation of toxicity and bioactivity predictive models of drugs. The contributions of these software tools tackled global problems, like drug repurposing during the coronavirus outbreak, and the direction toward personalized medicaments highlight their crucial role in the swift discovery of new treatments. In addition, computational tools are widely employed to enhance the drug formulations, which leads to discovering drugs with optimum pharmacokinetic and toxicity profiles. The difficulties in analyzing the multi-target binding behaviors and the limited success rates of the generated candidates in the experimental validations were the main existing limitations. However, the steep development in the field of artificial intelligence and the hybrid biochemical-computational approaches provided promising horizons to tackle these limitations. Chemical computational tools significantly affect the future of pharmaceutical research by boosting the drug discovery process toward affordable and efficient medicaments.

Keywords: computational chemistry; docking; drug discovery; molecular dynamic; pharmacophore

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1. Introduction

Drug discovery is a budget-draining and time intensive process that entails the investigation of academic knowledge, clinical trials, and regulatory authorization to ensure the safety and effectiveness of the new medications. The process is protracted and may extend over many years, with no absolute guarantee for success, as a wide range of candidates may not be able to complete their journey toward the pharmacy shelves[1]. Notwithstanding the obstacles of drug discovery, it is a vital aspect of the healthcare sector since it generates medications that can eradicate diseases, alleviate symptoms, or improve medical conditions[2,3]. Antibiotics, for instance, altered the way infectious diseases are treated forever, and recent advances in

cancer immunotherapy have given hope patients whose diseases were thought to have no possibility of remission[4,5]. Typical steps in the drug discovery process include validating the target, finding the lead compounds, refining and optimization of these compounds, and finally, moving on to preclinical research and clinical trials[6].

The drug discovery pipeline is presently experiencing significant transformations and facing four primary challenges. First, the progress in genomes and structure-based methodologies has led to a decrease in the accessibility of feasible pharmacological targets[7]. Second, there is an increasing emphasis on maximizing the return on investment throughout the entire pharmaceutical research process[8]. Third, there is a growing emphasis on ensuring safety, effectiveness, and pharmacokinetics in the early stages of lead discovery[9]. Fourth, the transition from conventional combinatorial chemistry to more focused and strategic diversification techniques[10,11].

Computational chemistry is a branch of chemistry that leverages computer simulation to solve complex chemical problems. It plays a crucial role in the molecular-level analysis of biological systems by focusing on an understanding of small molecules, drugs, and complex molecular systems, such as DNA, proteins, and other macromolec[12,13]. The drug discovery process is a complex interdisciplinary endeavor that often combines principles from chemistry, biology, and pharmacology[14]. By employing computational tools, researchers can predict the molecular attributes and unmask potential drug candidates more efficiently[15,16]. Furthermore, these tools will reduce the time and resources typically required for experimental testing. This requires close collaboration between medical scientists and researchers with expertise in multiple disciplinary areas[17].

This review aims to explore the crucial role of computational chemistry in accelerating the drug discovery process. It provides an overview of the evolution and application of computer-based tools in predicting new drug candidates, with examples of modern tools and techniques. Furthermore, the review discusses the impact of computational methods on drug discovery and offers insights into future perspective in this rapidly advancing field.

2. Drug discovery strategies

There are numerous and diverse strategies to discover new drug candidates. Chemical scientists and those interested in this field actively search for sources of medically related compounds in every region of the world. Generally, the strategies of drug discovery can be divided into traditional ones, those that depend on natural product screening and serendipitous discoveries, and modern or computer-based strategies[18,19].

2.1. Traditional drug discovery process

In the early stage of the drug discovery process, potential lead compounds are generally identified through high-throughput screening of a large compendium of synthesized or natural compounds[20,21]. This process starts by exploring thousands to millions of chemical frameworks to identify ones that showed desired biological activity; these are called the lead compounds. Once lead compounds are characterized, their structural frameworks are optimized to enhance their binding affinity and selectivity for their target macromolecules[22,23]. Importantly, these lead compounds must exhibit acceptable selectivity and specificity towards their target macromolecules while maintaining no affinity or activity towards other targets. Sensitivity issues are also crucial, requiring that these leads have significant activity at small doses to minimize their side effects as much as possible[24,25]. Additionally, these compounds must have eligible pharmacokinetic properties, such as a suitable elimination rate and plasma half-life, to ensure applicable drug administration. Other frameworks, those that failed to fulfill the requirements, were filtered out[26,27]. These steps are outlined in **Figure 1**.

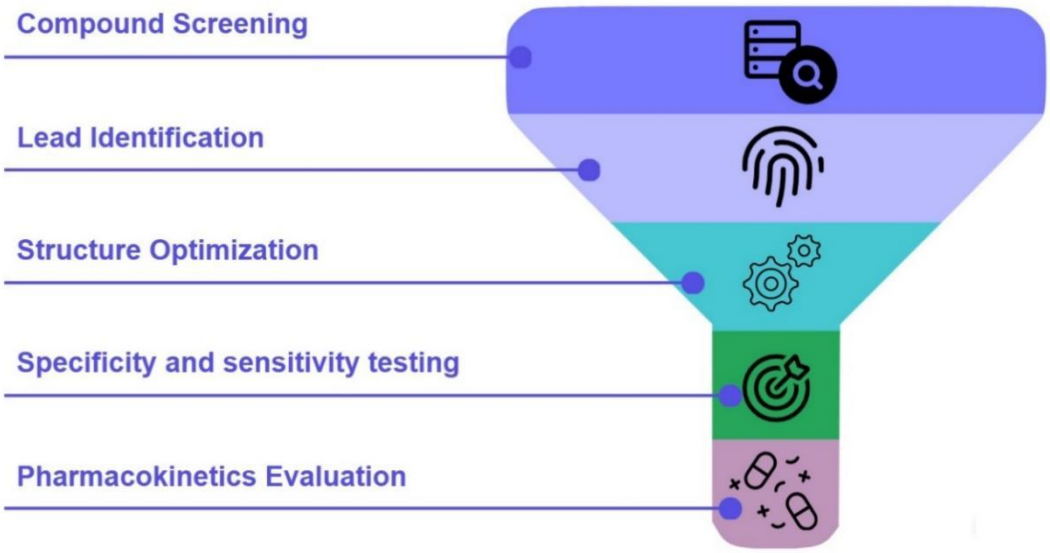

Figure 1. Traditional drug discovery process.

Many challenges are encountered in the traditional drug discovery process; these include time, effort consumption, elevated costs, and poor success probability[28]. Many of the explored frameworks may fail during lead optimization or investigational phases throughout the process, owing to their bioavailability, specificity, or their unfavorable pharmacokinetics[29,30]. Furthermore, this process depends mainly on the trial-and-error approaches, which can ultimately lead to inefficiencies. Therefore, it has become important to employ the step revolution in computational programs and tools to solve these encountered issues[31,32].

2.2. Role of computational chemistry

There is a wealth of challenges associated with the discovery and optimization of lead pharmaceuticals, from understanding disease biology to navigating the human use landscape[33,34]. Moreover, the process is costly and yields uncertain outcomes. New experimental techniques and tools, along with computational methods, are reshaping pharmaceutical drug discovery. The field of computational chemistry is a critical one in the drug discovery space[35,36]. These methods are broadly applicable to understanding and quantifying the behavior of biomolecular matter, changes to the properties of molecular matter in response to chemical modification, and how matter interacts [37]. In other words, computational methods are vital for understanding the chemistry that underpins biological behavior and how to leverage that knowledge for therapeutic benefit[38,39]. The field is now comprised of many scientific disciplines collaborating to understand how physical chemistry and chemical biology principles operate in concert to drive biological behavior[40,41].

3. Fundamentals of computational chemistry

Computational chemistry is based on the concept that employs mathematics, theoretical chemistry, and computer science to predict the behavior of certain chemical frameworks at atomic levels[42,43]. Electronic structure methods are the center of computational chemistry, which includes Hartree-Fock, post-Hartree-Fock, and density functional theory[44,45]. Researchers could predict the molecular behavior through dealing with the Schrödinger equation. As a result, researchers will gain a comprehensive understanding of energy states, electronic interactions, and reaction mechanisms[46,47]. Despite the challenges that computational chemistry encountered, the elevated accuracy of the forecasted information that these methods provide makes them essential and indispensable in practical methodologies[48,49]. The initial application of this field in practice was in the 1930s, while more scope widening and greater advancements in computational power occurred since the 1960s[40,50].

The applicability of the electronic structure methods in the larger molecular systems is computationally prohibitive. Therefore, classical mechanics, such as molecular mechanics, plays a crucial role in this field[51,52]. These approaches employ previously characterized parameters like bond angles, lengths, and torsions to predict the molecular behavior of the system. Taking small molecules (e.g., H_2O, CO_2, and NO_2) as an instance, the vibrational behavior of these molecules could be well predicted using harmonic 3N-6 normal coordinates[53,54]. Classical mechanics pick up the internal degrees of freedom for these systems, like angle bending and bond stretching. In addition, the potential for these vibrations to shift frequencies in response to structural framework alteration could also be described by classical mechanics[55,56].

The accurate ability of modeling small molecules like CO_2 and NO_2 flashlight the applicability of classical mechanics to predict, with minimal computational effort, the vibrational spectra[57,58]. In the case of condensed-phase systems, like molecular complexes in solvents, the prediction of the molecular behavior may be a challenging process with the computational models. For such cases, classical mechanics could provide affordable solutions, as it lacks the accuracy of the electronic structural methods in describing the electronic environments and the interactions of the systems[59,60].

Many computational tools, like Monte Carlo and molecular dynamics simulations, combine both the electronic structure and the classical mechanical methods to predict the molecular behavior. While Monte Carlo simulation statistically investigates molecular conformations, molecular dynamics investigates the dynamic behavior by exploring the movement of the molecule over a specified time period. These tools are considered valuable investigative tools for exploring the energy landscapes of large biological molecules such as proteins or enzymes[61–63].

The complexity of the molecular system in their condensed, solvent, or solid forms is the main persistent challenge that is encountered by these computational tools. Therefore, researchers attempt to create a hybrid approach that combines electronic structure and classical methods[64,65]. For practical application, it is important to have the ability to transform between the highly accurate electronic structure method for local interactions and the effective classical methods for macromolecular behavior[66,67]. Computational chemistry can reshape the field of drug discovery by grafting both of these methods into modern tools like machine learning and informatic-based techniques. Such grafting paved the way for researchers to link the theoretical and the experimental data, which enabled a comprehensive understanding of molecular systems and accelerated the steps of drug discovery[68,69]. The main differences between the two computational approaches are summarized in **Table 1**.

Table 1. Comparison between the electronic structure and the classical mechanic methods.

Comparison points	Electronic structure methods	Classical mechanic methods
Principle	Depend on dealing with Schrödinger equation to predict the molecular behavior	Based on previously characterized parameters like bond angles and lengths to predict molecular system
Accuracy	High accuracy for energy states, electronic interactions, and reaction mechanisms	Predict molecular behavior although it lacks the accuracy for electronic interactions
Scale	Suitable for small molecules due to computational processing requirements	Suitable for larger systems like macromolecules and molecular complexes
applications	Studying electronic interactions in details	Feasible for modeling macromolecules and predicting the vibrational behavior
Challenges	Costly and limited applicability for macromolecules	Lacks the accuracy to describe the electronic interactions in complex systems
Examples	Hartree-Fock, post-Hartree-Fock, and density functional theory	Molecular dynamics, mechanics, and Monte Carlo

4. Computational approaches in drug discovery

4.1. Molecular modeling

Molecular modeling is the cornerstone of modern drug discovery efforts. It often involves the use of computer-based methods to simulate drug interactions with biological targets[70,71]. These models aid researchers in comprehending the structural frameworks and behavior of different chemical and biological systems, providing essential insights for the development of viable medication candidates. Usually, the pipeline starts with making libraries of possible therapeutic molecules and biological targets. Next, the interactions between these molecules and targets are studied computationally[72,73]. Two common molecular modeling techniques are ligand-based drug discovery and structure-based drug discovery.

4.1.1. Ligand-based drug discovery (LBDD)

This model depends on the understanding of molecules (ligands) that are already proven to interact with a target. LBDD emphasizes the structural characteristics of these active ligands, those with potential biological activities, to build novel candidates exhibiting analogous biological action. After analyzing well-known active ligands to determine the characteristics that lead to their binding, researchers assess related substances for their capacity to bind to the target[74,75]. A prevalent method in LBDD is active-site modeling, which use three-dimensional representations of active drugs to emphasize common characteristics essential for binding to the target[76,77]. Active-site models are established through investigating the essential attributes of active chemicals and are utilized to forecast and identify novel possible candidates[78,79]. By directing the modification of chemicals from various chemical families, these models also make core-morphing easier, enabling researchers to investigate new chemical regions[80,81]. LBDD is particularly advantageous when the target protein's structure is unidentified, as it depends on ligand knowledge instead of direct structural data. The technique has demonstrated efficacy in directing the creation of novel therapeutic candidates by utilizing the binding characteristics of established active compounds[82,83].

4.1.2. Structure-based drug discovery (SBDD)

This model relies on the three-dimensional structure of the target macromolecule (receptor). Researchers could simulate the binding potential between the drug (ligand) molecule and the receptor by employing the computational techniques [84,85]. SBDD starts by building the three-dimensional structure of the target receptor, often required to be soluble [86,87]. Then, different groups of possible ligand molecules are docked with the target receptor using computers to show and measure the strength of their interaction [88,89]. To design more efficient candidates, the molecular geometry and the electronic characteristics of the binding sites (pockets) are investigated and analyzed[90–92].

In the field of drug discovery, SBDD occupies a wide area. One of the important examples was the identification of candidates that specifically targeted Mycobacterium tuberculosis proteins[93,94]. Researchers employ the SBDD models to investigate specific structural fragments that could be utilized as initial scaffolds for novel antimycobacterial agents[95–97]. The accelerated ability for screening and ranking the investigated chemical compounds, the enrichment of information about administration route, dosage, and possible side effects, and the streamlining of the process of drug developments are the main advantages that the SBDD modeling provides[98,99]. Collectively, these models render molecular modeling a potent and adaptable instrument in drug development, allowing researchers to devise and refine therapeutic candidates with enhanced efficiency and accuracy. **Table 2** presents a concise summary of the distinctions between LBDD and SBDD.

Table 2. Comparison between LBDD and SBDD.

Comparison points	LBDD	SBDD
Dependency	On the knowledge of active ligand	On the three-dimensional structure of the target macromolecules
Approach	Concentrate on modeling and analyzing documented ligands to characterize the binding features	Simulate and analyze the interaction between ligands and targets through employing computational docking
Techniques employed	Active-site modeling to predict new ligands	Molecular docking and analysis of biding pockets to recognize and optimize the ligand-receptor interaction
Advantages	Suitable when receptor's structure is unknown employing ligand data instead.	Effective when receptor's structure is known, permits direct investigation of binding site.
Core investigation	Facilities core-morphing to investigate new candidates by modifying existing bioactive ligands	Concern with structural fragments of the receptor to optimize the interaction or to discover novel candidates
Efficiency	Relatively faster when exploring known ligand; used for identifying wide spectrum of potential drugs	Provide enriched data about the ligand-receptor interaction, which aid in effective candidates seeking and ranking.

4.2. Quantum mechanics

One powerful approach to simulation is to use techniques of quantum chemistry to describe both the electronic structure and the bonding that occurs in the drug-target system[100,101]. Quantum chemistry, a subfield of computational chemistry, provides a powerful, accurate, yet computationally expensive means of modeling and designing molecules by solving Schrödinger's equation, which allows the quantum mechanical investigation of electronic states, molecular properties, and transitions[102,103]. Given a particular molecular structure, the main goal of quantum chemistry is the accurate determination of the electronic wave function. From this electronic wave function, several important molecular properties can be obtained[104,105].

Generally, there are two main classes of quantum chemical calculations: the ab initio method and the density functional theory[106,107]. Both of these calculations enrich researchers with comprehensive information about the reaction reactivity by exploring energy diagrams, reaction pathways, and electrical features[108,109]. In addition, quantum mechanics permit the computation of different electronic descriptors, like polarizability, electronegativity, and ionization potential, as well as chemical hardness and softness. With the aid of these descriptors, the relation between them and the training set's reactivity can be easily understood[110,111].

4.3. Virtual screening techniques

Researchers utilized various tools and techniques to discover potential drug candidates. Molecular docking and pharmacophore modeling were among the most important tools[112,113]. The easy reach of large libraries of ligands and the crystal structures of different receptors permits the emergence of effective docking programs. By using scoring functions, these programs can predict the strength of ligand-receptor interactions[114,115]. Receptors are chosen based on their well-established roles in disease mechanisms, availability of high-resolution crystal structures from databases like the Protein Data Bank, and their suitability for computational modeling. Structural integrity, binding site accessibility, and experimental validation from literature also play crucial roles in this selection process[116,117]. In addition, docking programs can deal with one or multiple targets at the same running time. Although this aids in identifying chemicals that had the potential to bind and interact with multiple targets, it also increases the risk of off-target effects. On the other hand, the pharmacophore-based modeling relies on the data provided by documented ligands and voids complex receptor realignment[118,119]. The summarized steps for each tool are displayed in **Figure 2**.

4.3.1. Docking and scoring methods

This method simulates the potential interaction between ligands and their receptors to provide a general perspective about the ligand's biological activity. Based on their three-dimensional structures, docking evaluates the strength of interaction and creates forecasted models for potential candidates[120,121]. In addition, this method employs the receptor's geometry to design models that provide precise ligand-receptor interaction, as displayed in **Figure 2**. By offering detailed insight into the binding mechanism, the docking tools potentially accelerate the process of drug discovery[122,123].

4.3.2. Pharmacophore modeling

This model characterizes the geometric and the spatial properties that are essential for ligand-receptor interactions. Pharmacophore modeling aids in exploring similar compounds, evaluating chemical properties, and seeking new lead compounds[124]. Homology[125] or de novo modeling[126] is utilized to predict the active-site properties of uncommon receptors, as displayed in **Figure 2**. The application of this model has mainly focused on finding new candidates for the most challenging pathogens, like Plasmodium[127], Trypanosoma[128], and Schistosoma mansoni[129].

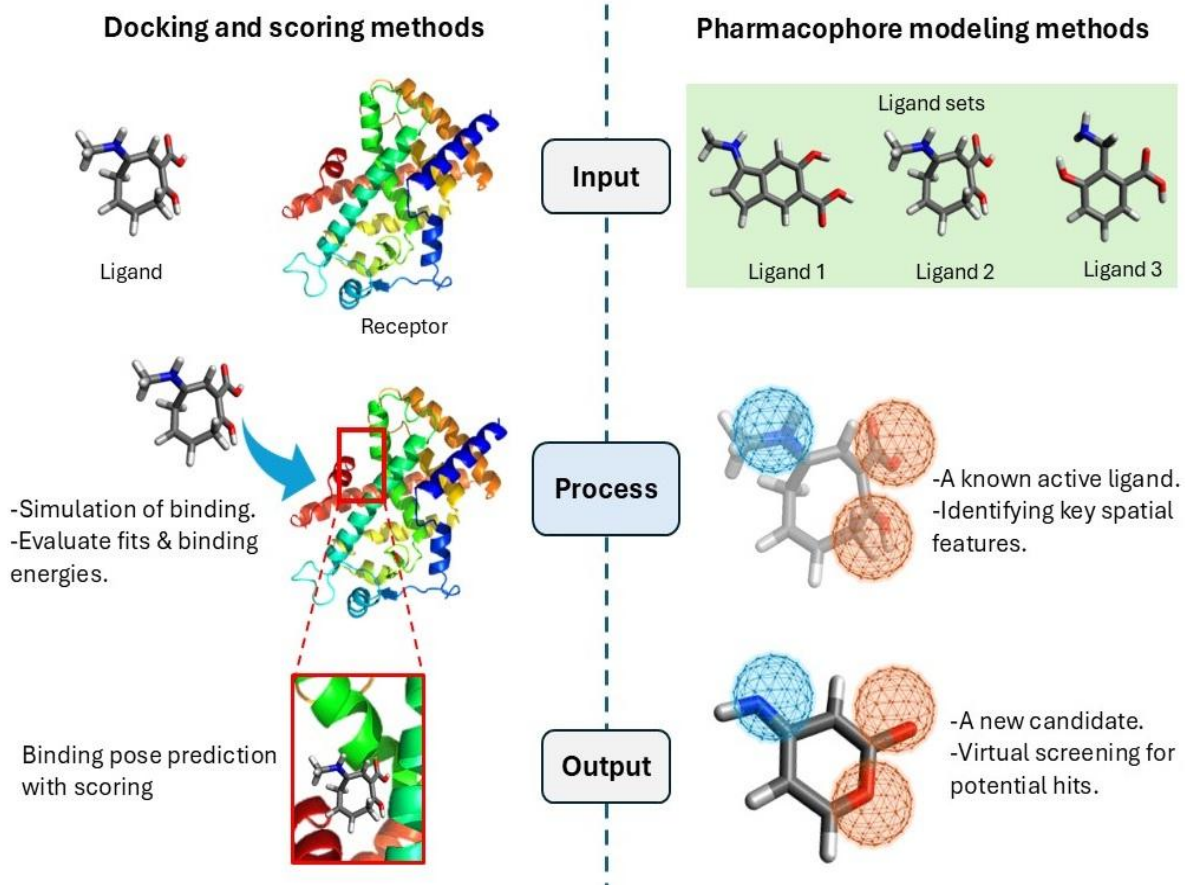

Figure 2. The summarized steps for docking and pharmacophore modeling methods.

4.4. Molecular dynamic simulations

Molecular dynamics (MD) simulations are among the essential tools in computational chemistry that enriched researchers with detailed information about the biomolecular systems at the atomic level[130,131]. The strength of ligand-receptor interactions, molecular attraction/repulsion mechanisms, and receptor flexibility are the most important details provided by MD simulations[132,133]. These simulations are also utilized for quantitative investigations, like evaluations of binding affinities for certain ligands[134]. The increased

advancement in the MD tools facilitates the characterization of binding poses, reinforcing the concept of computational prediction in the field of drug discovery[135,136].

4.4.1. Principle of MD simulations

The principle behind this approach depends on force fields and atomic models to assess the energy of the biomolecular system. The assessment starts with a computational calculation of the applied forces on each individual atom[137,138]. After that, loopingly dealing with Newton's equations of motion to forecast the trajectories of atoms over a specified time period[139,140]. The system's potential energy is described, by the force fields, as an integration of van der Waals, electrostatic, and bonded terms. The simulation's accuracy relies on the properties of the force field parameters[141,142]. These parameters determine the stability of the ligands' conformations and characterize the potential energy of the biomolecular system. The higher the optimization of the force fields, the more robust the forecasting capabilities, as those systems that craft the density functional methods and the atomic point charges[143,144].

4.4.2. Advancement and limitation in MD simulations

The classic MD simulation tools provide dynamic simulation for the biomolecular system in a nanosecond time scale. Now, the recent versions of offer simulation periods that extend to microsecond time scales[145,146]. This extension in the time scale will offer a comprehensive understanding of the dynamic behavior of the investigated biomolecular system. However, this time extension requires more efficient computers that could process the data in a proper way[147,148]. The efficiency and accuracy of these models are both limited by how well the underlying parameters are defined[149,150]. The more rapid the development of computer efficiency and algorithms, the more optimized the force fields will be, which aids in higher predictive power of the MD simulations and makes them an indispensable tool in the field of drug discovery[151,152].

4.4.3. MD simulation’s tools and data analysis

The most popular in silico simulation tools and programs for MD simulations are AMBER, GROMACS, CHARMM, and NAMD. Because it offers the most optimal FF99SB force field, AMBER is a beneficial tool for simulating peptides, proteins, and nucleic acids[153]. GROMACS is also appropriate for the simulation of nucleic acids[154] and polypeptides[155]. as well as oligopeptides and lipid molecules[156]. It is widely believed that CHARMM is an effective tool for simulating enzymes and other macromolecules[157]. Lastly, NAMD's efficiency in parallel processing makes it an ideal tool for large-scale biomolecular research[158]. Several visualization tools, including Chimera and PyMOL, are available to help make sense of the data and molecular trajectories that these programs offer[159,160].

The data of MD simulations are provided as graphical charts that reveal the behavior of the biomolecule under investigation over the specified time period. The most valuable charts are the root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), and hydrogen bond (H-bond) charts[161,162]. The atomic stability of the system is usually tracked by the RMSD chart, while the RMSF chart aids in the recognition of flexible regions in the biomolecules and the identification of active sites[163,164]. System compactness-related data are provided by the Rg charts, and the H-bond analysis aids in the evaluation of the ligand-receptor complex interactions[165,166]. **Figure 3** shows the MD simulation process, outlining the key steps involved in computational modeling of biomolecular systems. The process begins with input preparation, including the selection of the protein structure, ligand, solvent, and necessary charges. A suitable force field, such as ff14SB, CHARMM36, AMBER96, or FF99SB, is then assigned to define atomic interactions. The simulation itself is conducted by solving Newton’s equations of motion through iterative time steps. Finally, the results are analyzed using key metrics such as RMSD for structural stability, RMSF for residue flexibility, Rg for molecular compactness, and hydrogen bonding interactions, providing crucial insights into biomolecular behavior. These metrics, together with the molecular visualization, provide

a deep insight into the dynamic features of the investigated biomolecular system, which makes the MD simulations a valuable tool in the field of drug discovery[167–169].

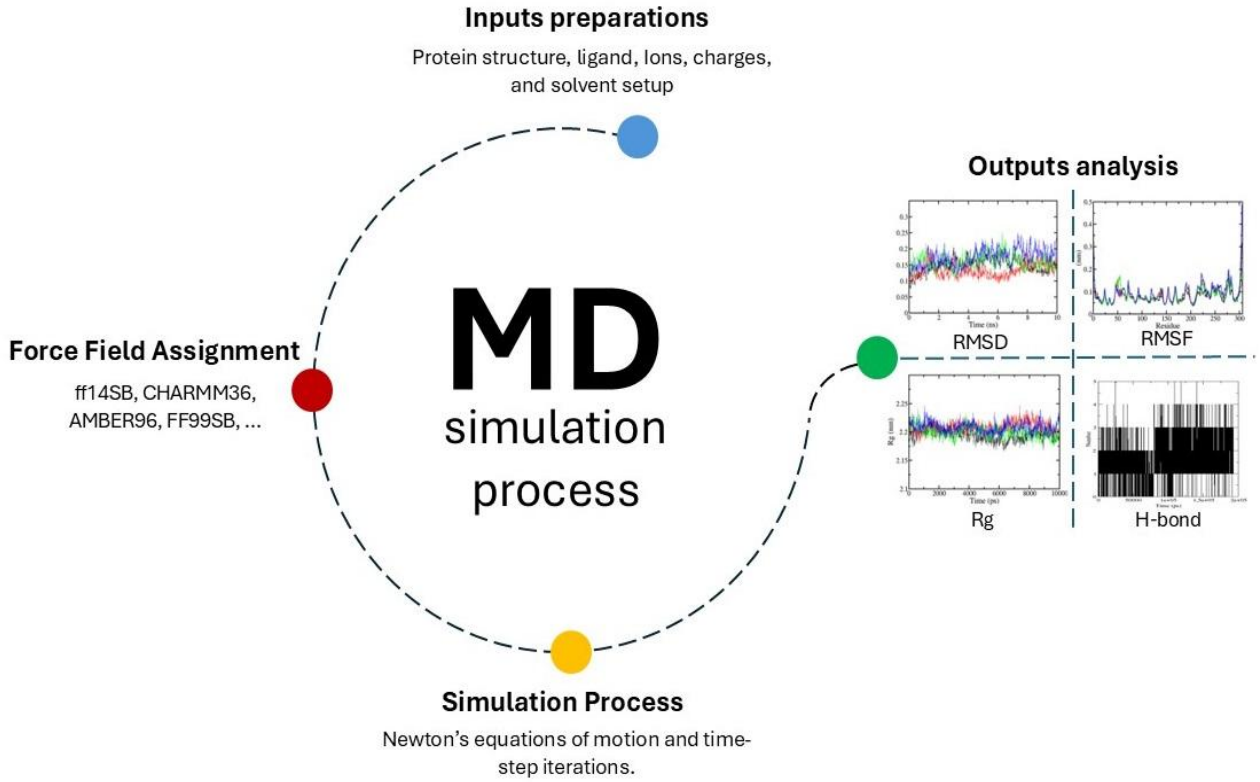

Figure 3. The main components of MD simulation process.

4.5. Quantitative structure activity relationship (QSAR)

QSAR is a research area in chemistry where the total set of data on physical and chemical properties, reactivity, or biological activities of compounds is used to build models using statistically correlated molecular descriptors[170,171]. The resulting model can be used for a variety of purposes, including predicting new biological activity or prioritizing a set of compounds for biological testing. As such, QSAR is an essential tool in the chemical, pharmaceutical, and materials industries, aiding various decision-making processes in chemical and materials design and application[172,173]. QSAR techniques are based on the assumption that chemically and physically similar compounds have a similar biological activity. Therefore, either experimental or calculated molecular descriptors can be employed in a QSAR model based on the similarity of compounds[174,175].

Statistically, QSAR uses the system data to build a predictive model for the system of interest. For any given set of experimental data, there is a unique set of parametrized equations that can fit it[176,177]. These equations can be used to predict selectivity and to help deduce the mode of action, i.e., to provide the physicochemical rationalization of the results, which provide powerful guidance for medicinal chemists in the design and optimization of other specified structural requirements[178,179]. QSAR models are commonly applied to estimate the toxicological profile of compounds during their chemical assessment for regulatory purposes, which is especially relevant to the pharmaceutical industry[180,181].

4.5.1. Principle of QSAR

QSAR tries to model responses based on chemical structure. The assumption is that similar chemical compounds have similar biological activity. This model is a chemically informed isomorphism assumption[182,183]. Mathematically, compounds are posited to dwell near points in a metric environment. The

transition from biological responses to chemical descriptors is accomplished predominantly through descriptor calculations. Therefore, a person who trusts the model also trusts the descriptors[184,185].

The cornucopia of QSAR approaches has limited the enthusiasm for this area and its use in practice. They fall into the standard setting and the variant flotsam and jetsam setting; there's essentially no form of QSAR that hasn't been thought of[186,187]. QSAR is the flipside of finding any dependence, i.e., many regressions, in the betting problem. QSAR searches for chemical insight in the fundamental pharmaceutical research setting[188,189]. These approaches are by no means without their merits. Furthermore, they benefit from economies of scale. Regrettably, they are available in a large-scale format[190]. The steps of QSAR modeling are outlined in **Figure 4**.

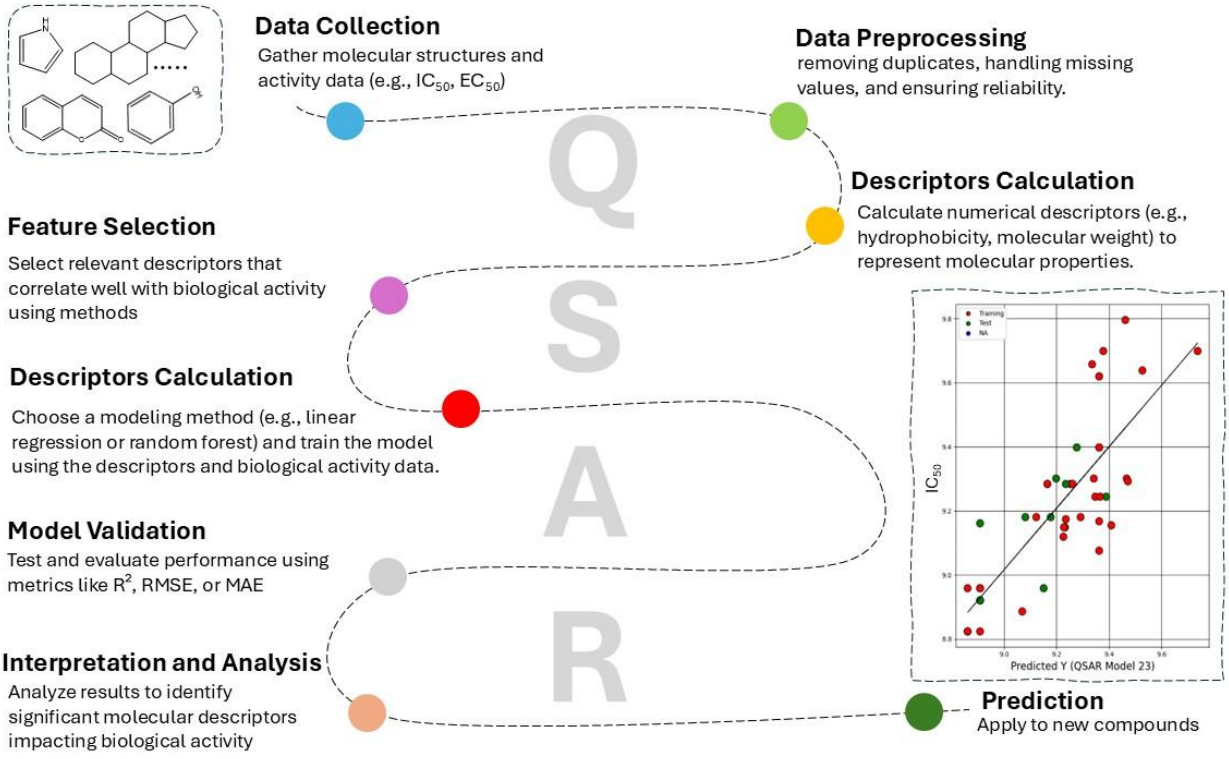

Figure 4. The steps of QSAR modeling.

4.5.2. Application of QSAR in drug discovery

The success story of computational chemistry is now very well recognized in drug discovery[191,192]. It contributes to the drug discovery cycle mainly in two ways: accelerating the drug discovery process by taking sick molecules out from the broad screening list and validating the hit list before taking them through *in vitro* or *in vivo* assays, thus resulting in significant economic paybacks[193,194]. The screenings of millions of virtual compounds not only identify leads from among the vast number of potential candidates but also allow a study of the structure–activity relationship and the interactions of small molecules with the active sites[195,196]. Computational methods also play a vital part in predicting the pharmacokinetic and pharmacodynamic properties of existing molecules to see if they are lipophilic or polar enough, if they have hydrogen bond donor and acceptor functionalities, and their acceptability for further dosage determinations[197–199].

4.6. Machine learning and artificial intelligence

Machine learning refers to methods that enable computers to "learn" from large datasets and evolve their representations of relationships in the data. Trained machine learning models can then make predictions for new data, providing the predictions are within the scope of the training data[200,201]. Machine learning and artificial intelligence in general have shaken the technology world in recent years, with a broad range of

successful applications[202,203]. As there is a large amount of interaction between the structural properties of the compounds and their bioactivity. These methods can also be very relevant for drug discovery[204,205]. The methods in machine learning include visual searching of molecular databases, and applications of machine learning within these fields have seen significant growth over the last decade[206]. Machine learning often finds its place in identifying patterns in chemistry, primarily helping to model bioactivities of small molecules using molecular descriptors, fingerprints, and/or systems like images[207,208]. Machine learning applications are typified in the QSAR field and in the prediction of pharmacokinetic/toxicity properties of drug molecules[209,210].

4.6.1. Types of machine learning algorithms

Machine learning algorithms make a qualitative transformation in the field of drug discovery. These algorithms expedite recognition of potential drug candidates through rapid analysis of complicated data records[211]. In general, machine learning algorithms are classified into three groups: supervised, unsupervised, and reinforcement learning algorithms. For labeled data records, like molecular descriptors in relation to known bioactivities, it is prudent to apply supervised learning algorithms to predict features such as efficacy, toxicity, and binding affinities for new chemical compounds[212]. Contrastly, for unlabeled data records, the application of the unsupervised algorithms is crucial, like grouping chemicals with identical features or diminishing the distraction of large screening records to permit easier analysis and visualization[213]. The last algorithm is usually employed for two purposes: (a) positively tuning the molecular design process, as the chemicals are loopingly created, and (b) optimizing the molecular structure of the bioactive scaffolds to maximize the potency and synthetic feasibility[214]. The detailed comparison between the three algorithms is listed in **Table 3**. Collectively, these algorithms decreased the obstacles that were encountered during the drug discovery process.

Table 3. Comparison between types of machine learning algorithms.

Comparison points	Supervised	Unsupervised	Reinforcement
Purpose	Predict specified features of chemicals	Recognize groups in chemicals data records	Aids in molecular designing and optimize molecular scaffolds to maximize efficacy
Training data	Labeled data records	Unlabeled data records	Performance-oriented rewards
Application	Predict pharmacokinetic / toxicity features	Grouping identical chemicals and aid in easier analysis	Discovering novel candidates with optimal features
Advantages	Accuracy of prediction	Recognize novel correlations in data records	Create novel candidates
Limitation	Necessitates costly labeled data records	Lack outputs interpretations	Necessitates efficient computational power and well-recognized rewards criteria

4.6.2. Applications in drug discovery

The real revolution in the drug discovery field was initiated by the advancement in machine learning and the artificial intelligence programs. These advancements allow for more precise and proficient methods to identify the lead compounds[215]. The involvement of machine learning and artificial intelligence programs in virtual screening has a significant impact on accelerating drug discovery[216]. This results in a reduction in the number of in vitro and in vivo experiments required to identify and assess compounds with promising drug eligibility features as potential lead compounds[217,218]. In addition to the advancement in the virtual screening, cheminformatics becomes crucial in the field of drug discovery. Cheminformatics boosts the process of drug discovery by its incredible ability to deal with and analyze huge data records[219]. Furthermore, cheminformatics employed reaction modeling techniques, molecular structure representations, and chemical feature calculations to aid in chemical selection and optimization[220]. Hybridized approaches of

machine learning, artificial intelligence, and cheminformatics permit the proficient recognition of the bioactive chemicals and forecasting molecular features. Such hybridized tools steeply accelerate the drug discovery process[221,222].

5. Computational chemistry in medicinal practice

Currently, a sizable portion of the drug discovery sector is devoted to computational chemistry, which attracts researchers with data that allows them to forecast molecular behavior and improve drug prospects. In medical practice, computational chemistry become indispensable tool that has various application in different medical aspects[223]. The main contributions of computational chemistry could be outlined in its success in addressing global health challenges[224]. The most important applications are outlined in **Figure 5**.

5.1. Drug repurposing

The worldwide outbreak stemming from coronavirus brought attention to the crucial role of computational chemistry tools in boosting the process of drug discovery[225,226]. Drug repurposing, which deals with recognizing novel uses for established drugs in the markets, evolved as a quick and efficient method for developing viral-fighting agents[227]. Artificial intelligence played a crucial role in accelerating this process by integrating predictive models with computational chemistry techniques to identify potential drug candidates rapidly[228]. Tools of computational chemistry, like molecular docking and MD simulations, have been utilized to discover drug candidates that specifically targeted the coronavirus enzymes[229]. These approaches were further enhanced by Artificial intelligence-driven algorithms that improved the accuracy of molecular interactions and reduced the time required for screening potential therapeutics[230]. Virtual screening tools make it easy to quickly screen large chemical libraries[231]. These libraries include phytochemicals like coumarins[232,233], flavonoids[234], and alkaloids[235], which are known to fight viruses. Hybrid approaches that combine AI, machine learning, and computational chemistry have significantly improved drug discovery by refining molecular selection processes, optimizing docking scores, and predicting pharmacokinetic properties with higher precision[230]. Computational chemistry laid the groundwork for later validations *in* vitro and vivo by finding molecules that have drug-like features. These molecules will eventually help the global fight against this outbreak[236].

5.2. Personalized medicaments

The steep development in the genetic studies has established the foundations for personalized medicaments[237]. This concept means that a therapeutic agent would be tailored according to the distinct genetic map of each individual patient[238]. In this field, computational chemistry played a significant role by designing and discovering novel medicaments that selectively match with the genetic polymorphism that is responsible for underlying pathologies[239]. This selectivity diminished the possibility of unwanted effects and got rid of the time and cost wasted on experimental trials[240]. By crafting genetic data records with the computational tools, there is a significant improvement in terms of dose regimens adjustment, efficacy optimization, and enhancement of patient compliance[232]. In addition to the progress of the therapeutic outcomes, personalized medicaments also decrease the medical expenditure by reducing the utility of ineffective medicaments[241,242].

5.3. Miscellaneous applications

The tools and techniques of computational chemistry were employed in a wide spectrum of applications in medicinal practice. It plays a crucial role in the investigation of rare and uncommon illnesses by identifying potential medicines to treat conditions that lack funding or researchers' attention[243]. In cancer therapy, computational chemistry facilitates the design of selectively targeted drugs by simulating molecular interactions and behaviors between the drug and tumor biomarkers[244,245]. Moreover, these technologies

substantially aid in addressing the global challenge of antimicrobial-resistant microorganisms by finding possible targets for these pathogens[246]. Furthermore, computational chemistry has a clear fingerprint in forecasting the pharmacokinetic and toxicity profiles, improvement of medicament formulations, and the solubility and stability of the candidates. Computational chemistry has numerous applications, and these examples show how it may solve difficult problems and spur innovation in the pharmacy sector[247].

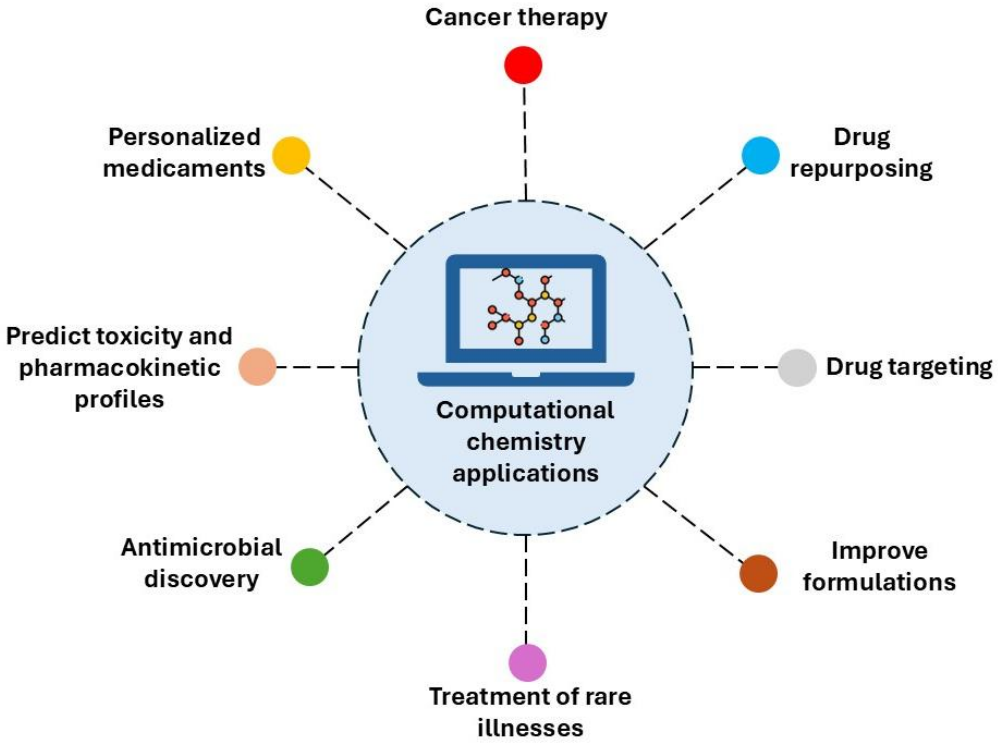

Figure 5. Applications of computational chemistry in medicinal practice.

6. Limitation and challenges in computational chemistry

While computational drug discovery has made steep progress, some issues still exist that compromise the dependability and usability of these approaches. The computational methods depend on approximations that might not completely replicate biological complexity like protein flexibility and solvation impacts[248]. To address these constraints, there are recent developments like ensemble docking, machine learning-driven scoring systems, and improved sampling techniques[249]. Considerable-scale virtual screening and high-resolution simulations also need considerable computational resources, which presents difficulties for research groups without access to high-performance computing. Potential fixes have been explored, including the integration of cloud computing, GPU acceleration, and prediction models driven by artificial intelligence[250]. Furthermore, computational forecasts call for experimental validation, which can be time-consuming and expensive; some expected drugs fail to show promised action in vitro and in vivo. Hybrid methods, those combining computer forecasts with automated high-throughput screening, are in development and expected to solve these concerns[251]. Challenges in biased datasets, overfitting, and lack of interpretability abound in artificial intelligence-driven drug discovery as well. Efforts in explainable artificial intelligence, data augmentation, and federated learning are strengthening these approaches' openness and resilience. Still major issues are ethical and regulatory ones like data privacy, repeatability, and artificial intelligence-generated molecular evaluation[252]. These days, regulatory authorities are looking at systems stressing openness, repeatability, and ethical norm compliance. Although these difficulties still exist, constant developments in computational techniques, artificial intelligence, and integrated approaches are gradually conquering these constraints. Refining prediction accuracy, enhancing computing efficiency, and

boosting experimental validation procedures will help to accelerate the identification of new drug candidates, hence defining the future of computational drug development[253].

7. Conclusion

Computational chemistry now occupies a substantial area in the field of drug discovery that recruits researchers with data that enable them to predict molecular behavior and refine drug candidates. Consequently, there is a significant reduction in time and cost that is associated with conducting traditional experimental methods. By employing the tools of computational chemistry—molecular docking, pharmacophore modeling, MD simulations, QSAR, and virtual screening—computational chemistry becomes able to recognize drug candidates with promising bioactivities. Our review highlights how these methods contribute to target identification, lead optimization, and pharmacokinetic profiling, ultimately accelerating drug discovery process. It provides significant data that enables a comprehensive understanding of the pathogenesis of the disease, boosting the process of drug design, and facilitates the converting of the theoretical data into real candidates, those ready for experimental validation. The horizon of the drug discovery process will mainly depend on the updated computational tools and techniques. These techniques are expected to be able to characterize compounds that are efficient, target-selective, and absorbable, thereby enhancing the drug discovery process. Moreover, we have emphasized the growing role of artificial intelligence and machine learning in computational drug discovery, demonstrating their ability to refine molecular predictions, automate data analysis, and streamline drug screening. Hybrid approaches, which combine computational and pharmacological methodologies with machine learning and artificial intelligence, significantly enhance drug discovery efforts. This kind of hybridization is expected to accelerate the drug discovery pipeline, improve the success outcomes, and reduce the cost of experimental procedures. The integration of these tools into current drug discovery workflows is expected to bridge the gap between in silico predictions and experimental validation, ultimately leading to more effective and rapidly developed therapeutic solutions. Thus, the computational chemistry would be the primary motivator of the pharmaceutical sciences advancement in the foreseeable future.

Conflict of interest

The authors declare no conflict of interest.

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