

Review

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Review

# Integrating Computational Biology in Modern Drug Discovery: A Synergistic Approach of Structure-Based, Ligand-Based, and Network Pharmacology Strategies

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## Abstract

Computational biology has completely changed the paradigm of drug development, moving it from random screening to a logical, predictive science. Three fundamental computational approaches Structure-Based Drug Design (SBDD), Ligand-Based Drug Design (LBDD), and Network Pharmacology are integrated in this review's potent, synergistic framework. In order to uncover important treatment targets, we show how these approaches function together as a coherent pipeline, with Network Pharmacology offering a systems-level blueprint of disease mechanisms. This realization immediately drives LBDD for intelligent screening utilizing pharmacophore and QSAR models in the absence of structural data, and SBDD for atomic-level rational design in the presence of it. Importantly, we stress that the foundation of this integrated strategy is early and iterative *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling, which guarantees the development of molecules with the best possible safety and drug-likeness. A new era of effective, multifaceted pharmaceutical development is ushered in by this technique, which de-risks the discovery process and speeds up the time from target identification to viable lead candidate by combining different disciplines into a single workflow.

**Keywords:** molecular docking; molecular dynamic simulation; network pharmacology; structure-based drug design; ligand-based drug design

## 1. Introduction

The search for novel medicinal molecules is a difficult, expensive, and time-consuming process that has historically relied on high-throughput screening and chance discovery. However, the development of advanced algorithms and computing power has sparked a paradigm change and ushered in a period of logical drug design. Nowadays, computer-aided drug design, or CADD, is a crucial component of pharmaceutical research since it makes it possible to quickly identify and optimize lead compounds with increased accuracy and efficiency. These techniques serve as a potent filter by simulating molecular interactions *in silico*, identifying the most promising candidates for experimental validation and lowering the risk associated with the early phases of drug development [1,2].

Modern drug development uses a diverse computational toolkit that includes a number of complementary approaches. The foundational idea of Paul Ehrlich's "corpora non agunt nisi fixata"

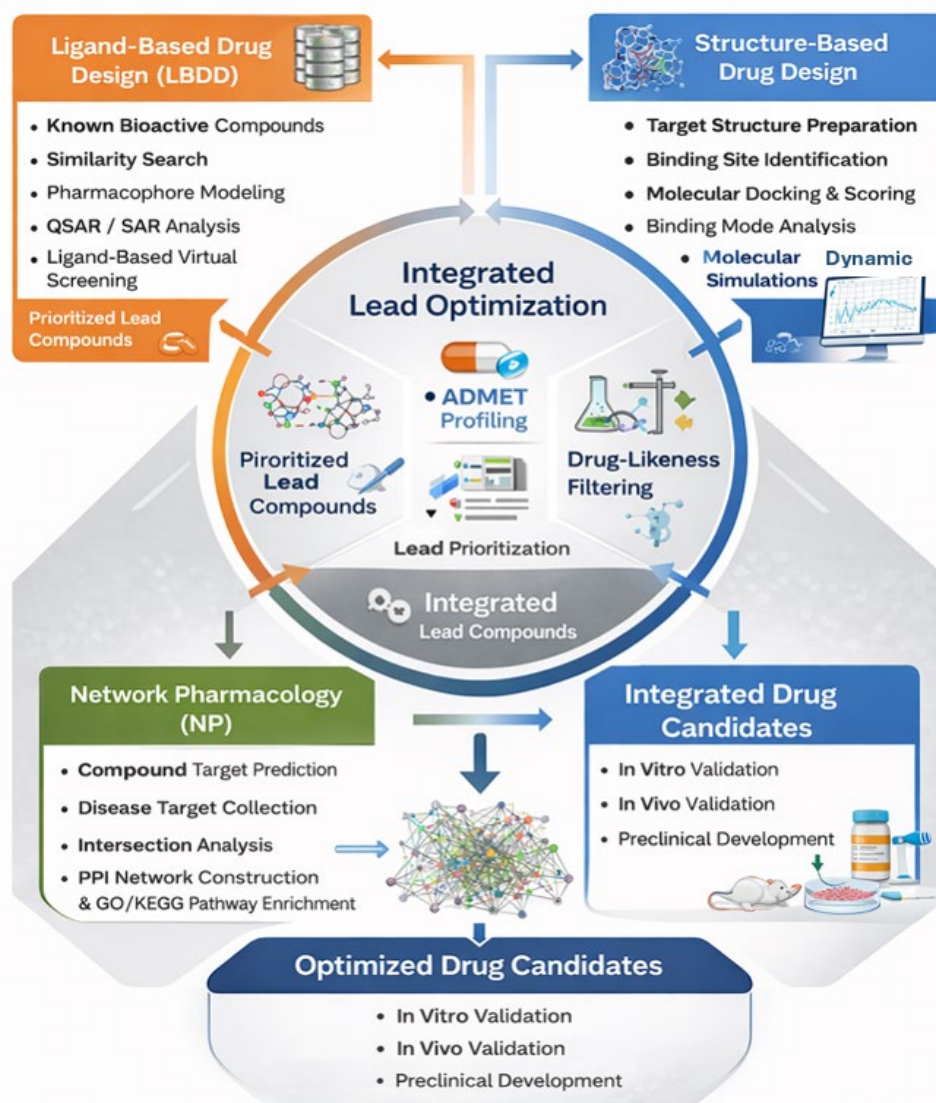
(substances do not act unless bound) is operationalized via Structure-Based Drug Design (SBDD) [3]. As it has been shown previously, it uses the three-dimensional structure of a biological target to predict how tiny molecules can bind to its active site, leading the logical design of powerful inhibitors [4–6]. Ligand-Based Drug Design (LBDD) provides an alternate route in the absence of structural information by using pharmacophore modeling and Quantitative Structure-Activity Relationship (QSAR) analysis to infer the key characteristics of bioactivity from known active molecules. A more comprehensive, systems-level viewpoint has been provided more recently with the emergence of network pharmacology. Understanding the polypharmacology of natural products is made easier using this method, which goes beyond the “one drug, one target” concept to map the intricate network of interactions between multi-target medications and disease-associated pathways [7,8].

Although these approaches are frequently addressed separately, their integration is where their real potential resides. A more robust and thorough discovery pipeline is produced via a synergistic strategy in which network pharmacology, LBDD, and SBDD confirm and inform one another. Additionally, the pipeline’s ultimate objective is to produce a viable medication rather than just a strong binder, therefore early use of *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling is essential for evaluating pharmacokinetics and drug-likeness.

This review offers a thorough examination of these fundamental computational techniques. From target preparation and molecular docking to dynamic validation using Molecular Dynamics (MD) simulations and LBDD, we will go into detail about the core ideas and procedures of SBDD. The network pharmacology concept and its use in deconvoluting intricate pharmacological effects will be discussed. Their significance in lead optimization will be emphasized by a rigorous examination of ADMET prediction systems. In conclusion, we will summarize how the combination of these fields, enhanced by AI and machine learning, is creating a new, more effective, and predictive future for drug discovery.

## 2. Structure-Based Drug Design

Structure-based drug design, or SBDD, is philosophically predicated on this claim. By evaluating their three-dimensional structures and determining binding affinity at the active site, SBDD forecasts and maximizes the interaction between a ligand and its target protein [9]. Computational techniques that are combined to evaluate binding energetics, conformational flexibility, and ligand-target interactions include molecular docking, fragment-based screening, and molecular dynamics (MD) simulations [10], as it is shown in Figure 1. The first FDA-approved HIV-1 protease inhibitors, Saquinavir and Amprenavir, which revolutionized HIV treatment in the 1990s, are among the many therapeutic advances that have resulted from this approach [4–6]. Moreover, SBDD has played a crucial role in identifying potent Pim-1 kinase inhibitors, offering promising therapeutic avenues for cancer treatment [11].



**Figure 1.** Synergistic computational workflow integrating ligand-based drug design (LBDD), structure-based drug design (SBDD), and network pharmacology (NP) for rational drug discovery. LBDD enables identification and optimization of lead compounds based on chemical similarity, pharmacophore features, and QSAR models. SBDD validates ligand–target interactions through molecular docking, binding mode analysis, and molecular dynamics simulations. NP provides a systems-level perspective by identifying disease-relevant targets and pathways.

### 2.1. Target Preparation

The Protein Data Bank (PDB), a valuable resource for structure-based drug design (SBDD), has grown significantly as a result of advancements in structural biology. However, many therapeutic targets' structures are still unknown due to experimental restrictions [12,13]. Computational techniques are used to forecast three-dimensional protein structures based on amino acid sequences. Tools like MODELLER and SwissModel are used in homology modeling, which is based on a template from a homologous protein (usually having a sequence similarity of >40%) [14,15]. When no template exists, ab initio methods such as I-TASSER and QUARK predict structures by identifying the most stable conformations [16,17]. The field has been revolutionized by AI-based tools like AlphaFold, which achieves near-experimental accuracy [18]. All predicted structures must subsequently be validated for quality using techniques including Ramachandran plots [19,20]. Consequently, obtaining and validating a precise 3D structure, whether determined experimentally or computationally, remains the essential foundation for successful SBDD.

## 2.2. Binding Site Prediction

The binding site of a protein is a small cavity or pocket where a ligand binds to activate, inhibit, or modify the protein [21]. Although co-crystallized protein–ligand complexes provide valuable structural information for SBDD, *in silico* methods can be utilized to predict potential binding sites in the absence of such information [22]. Several factors influence the accuracy of these predictions, such as template similarity and pocket size [23]. Van der Waals interaction energies between the protein and small probes are calculated by energy-based approaches such as Q-SiteFinder to identify and rank energetically favorable clusters as potential binding sites [24] (See Table 1). Alternatively, blind docking can be employed to search the entire protein surface for potential ligand-binding pockets in the absence of any prior knowledge. Blind docking can also uncover surprising binding mechanisms and interactions, despite its lack of precision [25,26]. The prediction of binding sites is supported by a number of computational methods, such as DeepSite, DoGSiteScorer, POCASA, Fpocket, RaptorX-Binding Site, COACH, and PocketDepth [27–33].

**Table 1.** List of ligand binding site prediction tools.

Name	Description	URL	Ref.
CASTp 3.0	Identifies and provides detailed geometric measurements of all potential surface pockets and interior cavities in a protein structure.	<a href="http://sts.bioe.uic.edu/castp/">http://sts.bioe.uic.edu/castp/</a>	[34]
SiteMap	Employs a grid-based method to locate and rank putative binding sites according to a proprietary score (SiteScore) that evaluates their ligand-binding suitability.	<a href="https://www.schrodinger.com/products/sitemap">https://www.schrodinger.com/products/sitemap</a>	[35]
Fpocket	An open-source, fast geometry-based pocket detection algorithm designed for large-scale binding site prediction.	<a href="https://github.com/DisorderedProteins/fpocket">https://github.com/DisorderedProteins/fpocket</a>	[29]
3DLigandSite	Utilizes homology modeling; it predicts a 3D structure for an input sequence and infers binding sites by mapping ligands from homologous protein-ligand complexes.	<a href="http://www.sbg.bio.ic.ac.uk/~3dligandsite/">http://www.sbg.bio.ic.ac.uk/~3dligandsite/</a>	[36]
PocketDepth	A geometry-based method that identifies ligand binding pockets by evaluating the depth and shape of protein surface cavities.	<a href="http://proline.physics.iisc.ernet.in/pocketdepth/">http://proline.physics.iisc.ernet.in/pocketdepth/</a>	[37]
DeepSite	A deep learning-based method that uses a 3D convolutional neural network to predict protein binding pockets.	<a href="https://www.playmolecule.com/deepsite/">https://www.playmolecule.com/deepsite/</a>	[27]
DoGSiteScorer	An automated pocket detection and analysis tool that calculates physicochemical properties and druggability of predicted binding pockets.	<a href="https://proteins.plus/">https://proteins.plus/</a>	[30]
POCASA	Predicts ligand binding sites by scanning the protein surface for regions that can accommodate a spherical probe.	<a href="http://altair.sci.hokudai.ac.jp/g6/Research/POCASA_e.html">http://altair.sci.hokudai.ac.jp/g6/Research/POCASA_e.html</a>	[33]
Q-SiteFinder	Identifies binding sites by computing the van der Waals interaction energies between the protein and a methyl probe.	<a href="http://www.modelling.leeds.ac.uk/qsitefinder/">http://www.modelling.leeds.ac.uk/qsitefinder/</a>	[24]
RaptorX-Binding Site	Predicts ligand binding sites using a combination of template-based and <i>ab initio</i> methods, leveraging deep learning for quality assessment.	<a href="http://raptorx2.uchicago.edu/">http://raptorx2.uchicago.edu/</a>	[31]
COACH	A meta-server approach that combines predictions from multiple methods (e.g., TM-SITE, S-SITE) to generate consensus ligand binding site predictions.	<a href="https://yanglab.nankai.edu.cn/COACH/">https://yanglab.nankai.edu.cn/COACH/</a>	[32]

### 2.3. Virtual Screening

Virtual screening (VS) is a powerful computer method used in medicinal chemistry to find potential lead compounds [38]. Using molecular docking, which ranks ligands according to binding affinity, it entails screening sizable databases of drug-like compounds against target proteins with known 3D structures [39]. In vitro tests are then used to validate the top-performing compounds, or “hits” [38]. There are two types of VS: structure-based (SBVS) and ligand-based (LBVS). LBVS uses molecular similarity or pharmacophore modeling to find active scaffolds and uses biological information to differentiate between active and inactive compounds [40]. On the other hand, SBVS relies on thorough structural data of the target protein to predict and assess ligand–protein interactions using docking algorithms with scoring functions. As shown in Table 2, compound libraries such as ZINC, PubChem, DrugBank, and ChEMBL are commonly used.

### 2.4. Molecular Docking and Scoring Functions

Molecular docking is a basic computational technique in structure-based drug design (SBDD) that forecasts the affinity and binding conformation (pose) of a small molecule (ligand) to a target protein [41]. This method is crucial for virtual screening (VS), which enables the efficient ranking of compounds from large libraries based on their predicted interactions with biological targets [42]. The most common approach, semi-flexible docking, permits ligand flexibility while preserving the protein’s rigidity; rigid docking treats both molecules as static, offering computational speed for high-throughput tasks; and flexible docking takes into account both the ligand and the protein’s conformational changes, offering the most realistic but computationally demanding simulation [43,44].

Docking programs use complex search techniques to navigate the large conformational space of a flexible ligand. Systematic approaches employ pre-generated conformational libraries or investigate rotational bonds in predetermined increments [45,46]. Monte Carlo simulations and genetic algorithms are examples of stochastic methods that incorporate random modifications that are either accepted or rejected depending on probability distributions [46]. Molecular Dynamics (MD) and other modeling approaches are used to achieve complete protein flexibility [43].

Scoring functions, which are mathematical models used to score postures and predict binding affinities, are essential to the precision of docking. They include functions that are empirical, knowledge-based, physics-based, and increasingly machine learning-based [47]. AutoDock Vina, Glide, and GOLD are well-known examples of conventional docking software (Table 3). Deep learning techniques are currently revolutionizing the field. For pose prediction and virtual screening, tools such as EquiBind, which makes direct “blind” predictions, DiffDock, a diffusion model that gives confidence estimates, and GNINA, which scores using convolutional neural networks, greatly outperform conventional techniques in terms of speed and accuracy [48–50].

**Table 2.** Overview of Publicly Accessible Chemical Libraries for In Silico Screening.

Database	Description	URL	Ref.
Zinc15	A comprehensive repository of over 230 million commercially available, “ready-to-dock” small molecules in 3D formats.	<a href="https://zinc15.docking.org/">https://zinc15.docking.org/</a>	[51]
PubChem	A vast public repository containing information on approximately 11 million unique chemical structures, alongside bioactivity data from high-throughput screening assays.	<a href="https://pubchem.ncbi.nlm.nih.gov/">https://pubchem.ncbi.nlm.nih.gov/</a>	[52]
ChemBridge	Provides a diverse collection of over 1.3 million small molecules, including both structurally diverse libraries and target-focused sets for screening.	<a href="https://www.chembridge.com/">https://www.chembridge.com/</a>	[53]

BindingDB	A specialized database focusing on measured binding affinities, containing data for over 1.2 million interactions between 520,000+ compounds and 5,500+ protein targets.	<a href="http://bindingdb.org">http://bindingdb.org</a>	[54]
Asinex	Offers a curated library of more than 90,000 lead-like compounds, designed for efficient virtual screening and hit identification.	<a href="http://www.asinex.com/">http://www.asinex.com/</a>	[55]

Table 3. Molecular Docking and Virtual screening Platforms.

Tool	Brief Description	URL	Ref.
AutoDock Vina	Known for its speed and accuracy; utilizes a hybrid global optimization algorithm and accommodates flexibility in receptor side chains.	<a href="http://vina.scripps.edu/">http://vina.scripps.edu/</a>	[56]
Glide	Employs hierarchical filters for rapid docking with multiple precision modes (SP, XP, HTVS) for scoring and ranking ligand poses.	<a href="https://www.schrodinger.com/glide">https://www.schrodinger.com/glide</a>	[57]
GOLD	Uses a genetic algorithm for conformational sampling and evaluates poses with functions like GoldScore and ChemScore.	<a href="https://www.ch.cam.ac.uk/computing/software/gold-suite">https://www.ch.cam.ac.uk/computing/software/gold-suite</a>	[58]
DOCK	A comprehensive suite that factors in desolvation, conformational entropy, and solvation, while supporting receptor flexibility.	<a href="http://dock.compbio.ucsf.edu/">http://dock.compbio.ucsf.edu/</a>	[59]
MOE	An integrated software platform featuring robust tools for molecular modeling, virtual screening, and structure-based design, including docking.	<a href="https://www.chemcomp.com/Products.htm">https://www.chemcomp.com/Products.htm</a>	[60]
HADDOCK	A highly adaptable approach for modeling diverse complexes, including protein-ligand, protein-protein, and protein-nucleic acid interactions.	<a href="https://wenmr.science.uu.nl/haddock2.4/">https://wenmr.science.uu.nl/haddock2.4/</a>	[61]
FITTED	A genetic algorithm-based program designed to handle macromolecular flexibility and the role of key water molecules in binding.	<a href="http://mglttools.scripps.edu/documentation/links/fitted">http://mglttools.scripps.edu/documentation/links/fitted</a>	[62]
FlipDock	Docks a flexible ligand into a fully flexible receptor binding site to address full conformational flexibility.	<a href="http://flipdock.scripps.edu/">http://flipdock.scripps.edu/</a>	[63]
LigandFit	Combines cavity detection with a Monte Carlo conformational search to generate and score ligand poses within active sites.	<a href="https://www.phenix-online.org/documentation/reference/ligandfit.html">https://www.phenix-online.org/documentation/reference/ligandfit.html</a>	[64]
pyDOCK	A fast, efficient web server for rigid-body docking using an advanced scoring function.	<a href="https://life.bsc.es/pid/pydockweb/">https://life.bsc.es/pid/pydockweb/</a>	[65]
ClusPro	An FFT-based server optimized for the rapid and accurate prediction of peptide-protein interactions.	<a href="https://cluspro.bu.edu/publications.php">https://cluspro.bu.edu/publications.php</a>	[66]
ZDock	Predicts protein-protein interactions using an FFT-based algorithm to explore rotational and translational space.	<a href="http://zdock.umassmed.edu">http://zdock.umassmed.edu</a>	[67]
PatchDock	Uses a geometry-based algorithm to predict structures of protein-protein and protein-small molecule complexes.	<a href="https://bioinfo3d.cs.tau.ac.il/PatchDock/php.php">https://bioinfo3d.cs.tau.ac.il/PatchDock/php.php</a>	[68]
FlexX	Utilizes a fragment-based method, placing core fragments in the binding site and reconstructing the complete ligand for scoring.	<a href="https://www.biosolveit.de/SeeSAR/#FlexX">https://www.biosolveit.de/SeeSAR/#FlexX</a>	[69]

Discovery Studio	A comprehensive modeling environment integrating docking with molecular dynamics, QM/MM, pharmacophore modeling, and QSAR.	<a href="https://www.discoverystudio.com/discovery.studio">https://www.discoverystudio.com/discovery.studio</a>	[70]
Surflex-Dock	A platform within the BioPharma suite providing tools for structure preparation, virtual screening, and ligand modeling.	<a href="https://www.biopharmics.com/">https://www.biopharmics.com/</a>	[71]
GEMDOCK	Uses a generic evolutionary method and a proprietary empirical scoring function for predicting ligand binding.	<a href="http://gemdock.life.nctu.edu.tw/dock/">http://gemdock.life.nctu.edu.tw/dock/</a>	[72]
EquiBind	A deep learning model that performs direct, “blind” prediction of ligand binding poses without the need for a traditional search procedure.	<a href="https://github.com/HannesStark/EquiBind">https://github.com/HannesStark/EquiBind</a>	[49]
DiffDock	A diffusion-based generative model for molecular docking that provides confidence estimates for its predicted ligand poses.	<a href="https://github.com/gcorso/DiffDock">https://github.com/gcorso/DiffDock</a>	[48]
GNINA	Utilizes convolutional neural networks (CNNs) for both pose prediction and scoring, offering high accuracy in structure-based virtual screening.	<a href="https://github.com/gnina/gnina">https://github.com/gnina/gnina</a>	[50]

### 2.5. Molecular Dynamics Simulation

In the 1970s, a computer technique known as molecular dynamics (MD) simulation was developed to model the intrinsic flexibility of proteins, which is crucial for processes such as ligand binding [73]. By resolving Newton’s equations of motion and forecasting the temporal evolution of a molecular system, MD simulations provide atomic-level insights into protein dynamics, conformational changes, and the stability of protein-ligand complexes [74]. As a result, MD is particularly helpful in drug development for docking posture validation, allosteric binding site identification, and virtual screening [75].

A typical process starts with setting up the system topology with tools like CharmGUI or AMBER, and then uses force fields like AMBER, CHARMM, or GROMOS to simulate atomic movements [76–78]. The produced trajectories are analyzed using software like Xmgrace to calculate stability metrics including radius of gyration, hydrogen bonding, Root Mean Square Deviation (RMSD), and Root Mean Square Fluctuation (RMSF) (Turner, 2005). The Molecular Mechanics/Poisson-Boltzmann Surface Area (MM/PBSA) and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) methods are commonly used for a more accurate determination of binding affinity because they more closely reproduce experimental results than conventional docking scores [80,81].

To get over computational constraints, the field is still developing. Longer, microsecond-scale simulations are now made possible by the use of Graphics Processing Units (GPUs) [82]. Additionally, by applying MM to the surrounding environment and QM to the reactive core, hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) techniques offer a balanced approach to investigating chemical reactions [83]. GROMACS, NAMD, AMBER, and CHARMM are well-known software programs that facilitate these sophisticated simulations [77,78,84,85].

Drug design has benefited greatly from the use of molecular dynamics (MD) simulations, which help to make sense of intricate biological processes. They are valuable because they can provide time-resolved, atomic-level information that is often unavailable through experimental methods. This ability is demonstrated in research on the effects of anticancer drugs, such as how cannabinoids inhibit glucose-6-phosphate dehydrogenase (G6PD) and how chemicals from *Withania somnifera* alter the KAT6A enzyme [86,87]. MD simulations provide dynamic information that is frequently unavailable to experimental approaches, making them a valuable tool for comprehending drug-target interactions and creating more potent treatments.

### 3. Ligand-Based Drug Design

A method called ligand-based drug design, or LBDD, is used when the active chemicals that inhibit a protein are known but its three-dimensional structure is unknown. This method is predicated on the idea that molecules with a high degree of physical and structural similarity are likely to exhibit similar biological activities [88,89]. Important LBDD methods that direct the creation of improved analog compounds and assist in identifying the characteristics that affect biological activity include pharmacophore modeling and quantitative structure-activity relationship (QSAR) modeling [90]. Compound libraries are usually screened to identify new candidates with similar features in order to identify known active compounds for the first time [12,91].

#### 3.1. Similarity Searches

The basis of ligand-based drug development is the molecular similarity notion, which maintains that molecules with similar structures are likely to have comparable biological functions. Using a known active component as a template, this technique uses similarity searches to identify new chemical entities with comparable characteristics [92,93]. This technique is crucial in situations where the target protein's structure is unavailable because it only needs ligand information. In order to find new bioactive ligands and improve their pharmacokinetic and efficacious characteristics, it is frequently employed for in silico screening [94].

#### 3.2. Pharmacophore Modeling

Pharmacophore modeling is one computer method for identifying the essential steric and electronic properties a drug need to bind a biological target [95]. When the three-dimensional structure of a protein is not available, this method which is based on the analysis of known active ligands is essential. The procedure entails creating a list of active substances and determining their common chemical characteristics, such as hydrophobic areas and donors/acceptors of hydrogen bonds that are essential for biological activity [96,97]. These attributes are then used to create a 3D query model based on these properties. Pharmacophore modeling uses specialized software such as like LigandScout, HipHop, HypoGen, and PHASE to generate 3D queries. These models can then virtually screen large compound libraries to identify novel chemical entities that share the essential pharmacophore features and are thus predicted to exhibit similar biological activity [98–100].

A major limitation of classical models is their static nature, which simplifies dynamic binding interactions. So, sophisticated methods like the “dynophore” have been devised to circumvent this. Molecular Dynamics (MD) simulations, which capture the dynamic aspect of binding, are included in the dynophore approach to offer data on interaction frequencies and a more accurate representation of the ligand-target complex [101].

#### 3.3. Quantitative Structure-Activity Relationship

The ligand-based Quantitative Structure-Activity Relationship (QSAR) technique creates mathematical models that link chemical structure to experimental activity by using molecular descriptors (MDs) or fingerprints (FPs) to predict biological activity. Support Vector Machines (SVM), Random Forests (RF), Polynomial Regression, Multiple Linear Regression (MLR), and Artificial Neural Networks (ANN) are a few of the machine learning (ML) and deep learning (DL) approaches commonly used in QSAR development [102]. In contrast to pharmacophore models, QSAR detects positive or negative effects associated to structure and quantitatively predicts activity. In drug design, QSAR is widely used for lead compound optimization, analogue activity prediction, and scaffold discovery. Through mathematical equations, classical 2D-QSAR links structure to activity using steric, electronic, and hydrophobic characteristics [103]. Force field-based models are used in advanced 3D-QSAR techniques, such as CoMFA and CoMSIA [104,105], which provide 3D contour maps for interpretation.

In pharmaceutical research and development, QSAR is an essential computational method [105,106]. While QSAR uses statistical modelling to connect physicochemical characteristics (such as molecular weight, lipophilicity, and electronic distribution) with bioactivity, pharmacophore mapping finds the structural elements that are responsible for biological activity (such as hydrogen bond donors/acceptors, hydrophobic regions, and aromatic rings) [107]. Model building and validation are made easier by contemporary tools such as MOE, Schrodinger, SYBYL-X, Open3DQSAR, Discovery Studio, and MOE (Table 4). By improving pharmacokinetics, potency, and selectivity, these models help optimize leads and cut down on time and expense associated with drug development [108]. One well-known example is the modelling of HDAC inhibitors, which are essential in cancer treatments, by combining QSAR with structure-based pharmacophores utilizing libraries of natural compounds [109]. Through ROC analysis and virtual screening, new HDAC-inhibiting scaffolds were discovered as a result of these efforts. The work showed how QSAR models anticipate analogue activity and direct hit-to-lead optimization [110].

#### 4. Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Properties

Pharmacology, the study of how drugs interact with biological systems, is the field that essentially directs drug discovery. Pharmacodynamics (PD), which studies how a drug affects the body, and pharmacokinetics (PK), which studies how the body affects a drug, specifically its Absorption, Distribution, Metabolism, and Excretion (ADME), are the two primary subfields of this science [2]. When the critical aspect of Toxicity is included, this full profile is known as ADMET. For a molecule to be considered a viable drug candidate, it must not only be active and specific in vitro but also possess favorable ADMET properties in vivo. A compound is unlikely to become a drug unless it is efficiently absorbed, adequately distributed, metabolically stable, and safely eliminated [111]. Therefore, optimizing ADMET profiles without sacrificing biological efficacy is a primary objective following lead compound identification. In the past, the main framework for forecasting drug-likeness was Lipinski's Rule of Five, which defined it by four important parameters: molecular weight (<500 Da), lipophilicity (cLogP <5), hydrogen bond donors (<5), and hydrogen bond acceptors (<10) [112]. These days, more advanced computational technologies frequently complement this early rule-based filtering. Nowadays, it's common practice to estimate thorough pharmacokinetic profiles early in the discovery phase using predictive platforms like SwissADME, PreADMET, ALOGPS, and DrugMint (Table 5).

**Table 4.** Software Tools for Quantitative Structure-Activity Relationship (QSAR) Modeling.

Tool	Description	URL	Ref.
QSAR ToolBox	An integrated platform that facilitates chemical grouping and read-across by combining experimental data, computational tools, and theoretical knowledge to identify structurally similar compounds.	<a href="https://qsartoolbox.org/">https://qsartoolbox.org/</a>	[113]
SYBYL-X	A comprehensive molecular modeling suite for small and macromolecular design, supporting lead identification and optimization through various computational methods.	<a href="https://chemweb.ir/downloads/sybyl-x-suite/">https://chemweb.ir/downloads/sybyl-x-suite/</a>	[114]
Open3DQSAR	A specialized tool for generating 3D-QSAR models through pharmacophore mapping and partial least squares (PLS) regression analysis.	<a href="http://open3dqsar.sourceforge.net/">http://open3dqsar.sourceforge.net/</a>	[115]

QSAR-Co	Enables the construction of multi-target classification QSAR models using machine learning algorithms such as Random Forest and Linear Discriminant Analysis.	<a href="https://sites.google.com/view/qsar-co">https://sites.google.com/view/qsar-co</a>	[116]
McQSAR	Utilizes a Monte Carlo-based genetic algorithm for the automated generation and optimization of QSAR models.	<a href="http://users.abo.fi/mivainio/mcqsar/index.php">http://users.abo.fi/mivainio/mcqsar/index.php</a>	[117]

**Table 5.** Web-servers for the prediction of the ADMET properties of compounds.

Name	Brief Description	URL	Ref.
SwissADME	Computes physicochemical properties and predicts pharmacokinetic (ADME) parameters.	<a href="http://www.swissadme.ch/">http://www.swissadme.ch/</a>	[118]
ADMETlab	A comprehensive platform for the systematic evaluation of ADMET properties.	<a href="http://admet.scbdd.com/">http://admet.scbdd.com/</a>	[119]
PreADMET 2.0	Predicts absorption, distribution, metabolism, excretion, and toxicity parameters.	<a href="https://preadmet.bmdrc.kr/preadmet-pc-version-2-0/">https://preadmet.bmdrc.kr/preadmet-pc-version-2-0/</a>	[120]
ALOGPS 2.1	Predicts key physicochemical properties like lipophilicity (LogP) and water solubility.	<a href="http://www.vcclab.org/lab/alogps/">http://www.vcclab.org/lab/alogps/</a>	[121]
DrugMint	Assesses the drug-likeness of small molecules using various screening rules.	<a href="https://webs.iiitd.edu.in/oscadd/drugmint/">https://webs.iiitd.edu.in/oscadd/drugmint/</a>	[122]
LightBBB	Predicts blood-brain barrier (BBB) permeability for chemical compounds.	<a href="http://bioanalysis.cau.ac.kr:7030/">http://bioanalysis.cau.ac.kr:7030/</a>	[123]
ProTox-II	A virtual lab for predicting the toxicity of small molecules, including organ toxicity.	<a href="http://tox.charite.de/prottox_II/">http://tox.charite.de/prottox_II/</a>	[124]
CardPred	Estimates cardiotoxicity risk by predicting hERG channel blockade liability.	<a href="http://bioanalysis.cau.ac.kr:7050/">http://bioanalysis.cau.ac.kr:7050/</a>	[125]
ToxinPred2	Predicts and assists in the design of toxic versus non-toxic peptides.	<a href="https://webs.iiitd.edu.in/raghava/toxinpred2/index.html">https://webs.iiitd.edu.in/raghava/toxinpred2/index.html</a>	[126]
ToxiPred	Predicts compound toxicity using quantitative structure-activity relationship (QSAR) models.	<a href="http://crdd.osdd.net/oscadd/toxipred/">http://crdd.osdd.net/oscadd/toxipred/</a>	[127]

## 5. Network Pharmacology

Network pharmacology provides a methodical framework for elucidating the complex mechanisms of bioactive compounds, particularly those included in herbal remedies, by means of a multi-step process that blends computer predictions with experimental confirmation [7]. Finding active compounds and their canonical SMILES structures from medicinal plants is the first step in the process, which involves collecting disease-associated genes from public sources and applying data mining. Then, transcriptome data analysis and computational target prediction are employed to find potential compound-target and disease-target interactions [128]. Venn diagrams are utilized to find common targets between chemicals and disorders as potential therapeutic targets, and statistical cutoffs are employed to find significantly connected genes [129]. Protein-protein interaction (PPI) networks constructed from these shared targets help identify hub genes and key active components that regulate disease-relevant biological pathways [130]. Subsequent network analysis, including topological assessment and functional enrichment analysis through KEGG and GO, reveals crucial subnetworks and pathways regulated by these targets [131].

Both experimental techniques and high-throughput in silico technologies are used to validate computational predictions. By forecasting binding affinities, molecular docking is essential for confirming ligand-target interactions and successfully bridging the gap between conventional and contemporary pharmacological techniques [132]. In addition, network pharmacology, fueled by the

rise of omics technologies (genomics, proteomics, metabolomics), presents a transformative approach to cancer drug discovery by overcoming the cost and time limitations of traditional methods [133]. This has been demonstrated in studies of *Prunella vulgaris* for breast cancer, which showed strong binding affinities of its active components to disease target. Similar results were observed with *Artemisia argi* against hepatocellular carcinoma and *Nauclea latifolia* against breast cancer [8,134,135]. Gene expression microarray analysis, supported by datasets from repositories like GEO, provides additional validation by assessing transcriptional changes across hundreds of genes under various experimental conditions [136].

## 6. Structure Framework of Computational Drug Discovery

Contemporary drug discovery is increasingly driven by integrated computational frameworks that unify multiple in silico strategies into a single, predictive pipeline (Figure 1). In this framework, network pharmacology provides a systems-level perspective by elucidating disease-associated molecular networks, identifying key regulatory targets, and capturing the complexity of polygenic and pathway-driven pathologies. This holistic understanding establishes a rational foundation for target prioritization and therapeutic hypothesis generation.

Building upon these insights, structure-based drug design (SBDD) is employed when high-resolution target structures are available, enabling rational ligand design through binding-site identification, molecular docking, and dynamic stability assessment. In parallel, ligand-based drug design (LBDD) complements this approach in scenarios where structural information is limited, leveraging known bioactive compounds to perform similarity searches, pharmacophore modeling, and quantitative structure–activity relationship (QSAR) analyses. The bidirectional integration of SBDD and LBDD ensures iterative refinement and cross-validation of candidate molecules.

Critically, early and iterative ADMET profiling is embedded throughout the pipeline to evaluate pharmacokinetic behavior, drug-likeness, and safety liabilities, thereby filtering out suboptimal candidates at the earliest possible stage. The synergistic integration of network pharmacology, SBDD, and LBDD substantially surpasses the predictive power of any single methodology, reducing attrition risk and accelerating the translation of molecular insights into high-confidence therapeutic candidates.

## 7. Critical Challenges

Despite tremendous progress, computational drug discovery still faces a number of important obstacles. The ability to accurately anticipate binding affinities is a major drawback. The scoring systems used to quantify binding free energy frequently lack the precision necessary to consistently rank ligands, resulting in false positives and negatives in virtual screens, despite the fact that molecular docking is quite good for posture prediction [47]. Furthermore, a significant obstacle is the dynamic nature of biomolecules by nature. The majority of docking procedures fail to capture the conformational changes and allosteric effects that are essential for binding and function because they regard the protein receptor as rigid or semi-flexible [137]. It is still computationally intensive and challenging to generalize to account for solvation effects and the function of important water molecules in binding sites.

In LBDD, the quality and quantity of training data have a direct effect on the prediction performance of QSAR and pharmacophore models. Because of its extrapolation challenges, these models often fail to accurately forecast the activity of compounds with novel scaffolds beyond the chemical space of the training set [106]. It is necessary to integrate and validate the enormous volumes of heterogeneous data from omics technologies in order to build physiologically meaningful and predictive network models in network pharmacology [133]. Lastly, although though ADMET prediction methods are very useful, their precision depends on the quality of the underlying data, and it is still a challenging task to predict complex in vivo phenomena from simple chemical structures, such as organ-specific toxicity and drug-drug interactions [124].

## 8. Conclusion and Perspectives

This study highlights the strategic value of integrating network pharmacology with ligand-based and structure-based drug design approaches to rationalize and accelerate early-stage drug discovery. By combining systems-level target identification with molecular-level interaction analysis, this integrated computational framework enables a more comprehensive understanding of compound–target–pathway relationships than any single methodology alone. Network pharmacology provides a holistic view of disease-associated biological networks and polypharmacological effects, LBDD facilitates efficient identification and prioritization of chemically relevant candidates based on known bioactivity patterns, and SBDD offers atomistic insight into binding modes, interaction stability, and target specificity. Together, these complementary strategies form a coherent and rational pipeline for lead identification and optimization in complex diseases.

Despite the strengths of this integrated approach, it is essential to recognize its inherent limitations. All predictions presented herein are derived from *in silico* analyses and should be interpreted as hypothesis-generating rather than definitive evidence of biological efficacy. Molecular docking scores and molecular dynamics stability metrics, while informative, do not directly translate into pharmacological activity or clinical benefit. Nevertheless, by narrowing the chemical and biological search space, this computational framework substantially improves efficiency and cost-effectiveness, thereby enabling more focused and rational experimental validation in subsequent *in vitro* and *in vivo* studies.

Looking ahead, the continued convergence of computational drug discovery with artificial intelligence and machine learning is expected to further enhance the predictive power and scalability of integrated pipelines such as the one presented in this work. Advances in deep learning–based docking algorithms, protein structure prediction platforms, and generative chemistry models are rapidly transforming virtual screening and lead optimization. The incorporation of dynamic interaction descriptors, such as MD-informed pharmacophores, along with multi-omics and single-cell data within network pharmacology frameworks, will enable increasingly precise characterization of disease mechanisms and therapeutic responses. Ultimately, the development of unified, end-to-end *in silico* platforms capable of jointly predicting target engagement, pharmacokinetics, safety, and efficacy holds the promise of reducing attrition rates and accelerating the translation of computational discoveries into clinically relevant therapeutics. In this context, the integrative strategy presented in this study provides a solid conceptual and methodological foundation for future computational and experimental drug discovery efforts

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