In silico docking and drug design of herbal ligands for anticancer property

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Abstract

In silico approaches have been widely recognized to be useful for drug discovery. Here, we consider the significance of available databases of medicinal plants and chemo and bioinformatics tools for in silico drug discovery beyond the traditional use of medicines. Whereas computational methods for molecular design are well established in medicinal chemistry research, their application in the field of natural products is still not exhaustively explored. The challenge is which selection criteria and/or multiple filtering tools to apply for a target-oriented isolation of potentially. The amount of available data on the biological activity of the investigated compounds (including herbal medicines) and the number of target macromolecules related to their therapeutic effects increase every year. At the same time, the pool of data on compositions of medicinal plants has also increased. Therefore, the need for use of in silico methods to determine the biological activity of medicinal plants is obvious.

In-silico studies are done to identify the exact target of the drug. Which finds a drug for the particular binding site and final stage animal testing can be done for obtaining a conform result. Specific software on a computer allows researchers to analyze enormous data without actually conducting a large number of experiments. It helps to give the existing information to model disease pathway and identifies precise targets of the selected drugs. Later stage in vivo and in vitro studies can be done for obtaining the confirmatory result.

Keywords: In-silico studies, cancer, docking, protein, herbal ligands

Introduction

Natural products have been used in folk medicine for thousands of years. One-third of the Indian population and more than 80% of the population uses herbal medicinal products to promote health and to treat common illnesses such as colds, inflammation, heart diseases, diabetes and central nervous system disorders. It is believed that plant and its chemical constituents interacting with human biological system by altering environmental stresses and adapt to these changes \[1\]. This type of adaptation is accompanied by unusual phytochemical diversity. These data confirm the assertion by Dhawan \[2\] that the study of plants, based on their use in traditional systems of medicine, is a viable and cost-effective strategy for the development of new drugs \[3\]. Because there are several thousand pharmacological targets and because most natural compounds exhibit pleiotropic effects by interacting with different targets, computational methods are the methods of choice in drug discovery based on natural products \[4\]. The use of chemo- and bioinformatics methods for the exploration of their pleiotropic pharmacological potential beyond the traditional uses may be possible with the availability of medicinal plant databases including data on chemical structures and therapeutic uses of phytoconstituents identified over the years from medicinal plants.

Docking

If the structure of the target has been solved at high resolution with X-ray or NMR and the molecular model of the binding site is precise enough, the best possible starting point in a structure-based drug design is the application of docking algorithms. Molecular docking is a
molecular simulation technique widely used to research the interaction between the ligand and target. The docking process is the virtual simulation of the energetic interaction between the ligand and the target, including the prediction of the best ligand conformation and orientation within the binding site [5].

Docking is a method that predicts the preferred orientation of one small molecule bound to a target, forming a stable complex. It consists of multiple steps. The process begins with the application of docking algorithms that pose small molecules within the active site of the target. Algorithms are complemented by scoring functions that are designed to predict the biological activity through the evaluation of interactions between compounds and potential targets. Thus, docking programs have mainly three purposes. First, docking programs serve to identify potential ligands from a library of chemical compounds. Second, they can predict the binding mode of potential ligands or known ligands. Finally, using the predicted binding pose, these programs calculate putative binding affinities used as a score to identify those compounds which are more likely to bind the drug target.

Docking programs have shown to be successful in screening large chemical libraries, reducing them into a more manageable subset that is enriched for binders. In cases of true interactions, the predicted ligand pose often correlates well with experimentally solved protein-ligand complexes. While structure-based methods have led to the identification of novel drugs, binding pose prediction is considered one of its strengths. 22 Since molecular docking plays a central role in predicting protein-ligand interactions it has been extensively used for drug hit discovery and lead Optimization [6-10].

Bioinformatics has, out of necessity, become a key aspect of drug discovery in the genomic revolution, contributing to both target discovery and target validation. The pharmaceutical industry has embraced genomics as a source of drug targets and as a corollary, has recognized that bioinformatics is crucial to exploiting the data produced on a genome-wide scale5. Computer-aided drug design (CADD) is a widely used term that represents computational tools and resources for the storage, management analysis and modeling of compounds. It includes development of digital repositories for the study of chemical interaction relationships, computer programs for designing compounds with interesting physicochemical characteristics, as well as tools for systematic assessment of potential lead candidates before they are synthesized and tested. Over the years, new technologies such as comparative modeling based on natural structural homologues have emerged and began to be exploited in lead design. These, together with advances in combinatorial chemistry, high throughput screening technologies and computational infrastructures, have rapidly bridged the gap between theoretical modeling and medicinal chemistry. CADD now plays a critical role in the search for new molecular entities6. Current focus includes improved design and management of data sources, creation of computer programs to generate huge libraries of pharmacologically interesting compounds, development of new algorithms to assess the potency and selectivity of lead candidates and design of predictive tools to identify potential ADME/Tox liabilities [7]. Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Computer - Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug - receptor interactions. One of those methods is called docking. The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions [8]. Molecular modeling technologies have mainly been developed during the past decades, due to the development of fast computers and are today essential tools in drug development used for protein structure determination, sequence analysis, protein folding, homology modeling, docking studies and pharmacophore determination [9]. Structure-based (direct) drug design is generally performed using a known 3D structure of a specific biological target [10]. Ligand-based (indirect) drug design to correlate physicochemical properties of compounds with their pharmacological activity and the calculated mathematical relationship can predict the activity of novel compounds [11]. Molecular docking is commonly used in the field of drug design to predict the binding of small molecules to biological protein targets. This method gives the possibility to study an active site in detail and can be used for hit identification, virtual screening, binding mode determination and lead optimization. Generally, the docking methodology is used to fit a compound into an artificial model or to a known three-dimensional binding site, which can be utilized to explore ligand conformation, orientation and feasible molecular interactions such as hydrogen bonding and hydrophobic interactions. Thus, molecular docking is a powerful tool for the design of ligands toward a specific protein target [12]. ‘Docking program’ is used to place computer-generated representations of a small molecule into a target structure in a variety of positions, conformations and orientations. Each such docking mode is called a ‘pose’. In order to identify the energetically most favorable pose, each pose is evaluated (“scored”) based on its complimentarily to the target in terms of shape and properties such as electrostatics. A good score for a given molecule indicates that it is potentially a good binder [13]. Docking explores the ways in which two molecules, such as drugs and enzyme receptors fit together and dock to each other well. The molecules binding to a receptor inhibit its function and thus act as drug. Complexes were identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations [14].

Ligand and structure-based methods

Evidence of computational drug design success in the field of drug development is reflected in a significant number of new drug entities that are currently in clinical evaluation. Computational drug design has emerged to harness different sources of information to facilitate the development of new drugs that modulate the behavior of therapeutically interesting protein targets. These computational approaches are classified mainly into two families: ligand and structure-based methods. Ligand-based methods use the existing knowledge of active compounds against the target to predict new chemical entities that present similar behavior [15-17].

Given a single known active molecule, a library of molecules may be used to derive a pharmacophore model to define the minimum necessary structural characteristics a molecule must possess in order to bind to the target of interest. Comparison of the active molecule against the library is often performed via fingerprint-based similarity searching, where the molecules are represented as bit strings, indicating the presence/absence of predefined structural descriptors [18]. In

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One of the advantages of artificial neural methods etc. is that they can be used to predict the structure of proteins co-crystallized with other ligands. In the absence of knowledge about the binding sites, cavity detection programs or online servers, such as POCKET [23], Surf Net [24-25], PASS [26] and MMC [27] can be utilized to identify putative active sites within proteins. Docking without any assumption about the binding sites is called blind docking.

Drug Design

Drug design, sometimes referred to as rational drug design (or more simply rational design), is the inventive process of finding new medications based on the knowledge of biological targets [28]. Rational drug design can be broadly divided into two categories: development of small molecules with desired properties toward targets, biomolecules (proteins or nucleic acids), whose functional roles in cellular processes and 3D structural information are known. This approach in drug design is well established, being applied extensively by the pharmaceutical industries. Another approach is development of small molecules with predefined properties toward targets, whose cellular functions and their structural information may be known or unknown [29]. The identification of a potential drug target is valuable and significant in the research and development of drug molecules at early stages. Due to the limitation of throughput, accuracy and cost, experimental techniques cannot be applied widely. Therefore, the development of in silico target identification algorithms, as a strategy with the advantage of fast speed and low cost, has been receiving more and more attention worldwide. It has been of great importance to develop a fast and accurate target identification and prediction method for the discovery of targeted drugs, construction of drug-target interaction network as well as the analysis of small molecule regulating network [30].

The acquisition of chemical compound information [31-32]

A thorough understanding of the effective compounds in medicinal plants is the key to the research and development of medicinal plants. Therefore, the collection of constituent information and the construction of the compound database are highly important for their application. The construction of a compound database can effectively manage the large quantities of compounds found in medicinal plants.

Collection of chemical compound information [33]

The information contained in a medicinal plant is the initial raw material for determining the basis of the herb’s pharmacological properties. Compound information was mainly collected from the following sources: (1) separation and purification of the compounds in a local laboratory; (2) literature reports; and (3) small molecule compound databases. Among these three information gathering pathways, the extraction of compounds in a local laboratory is the most direct and convenient method and can provide samples for later experimental studies. When a single compound is purified from herbs, the relevant information is collected such as its recording number, CAS number, name, source plant, extractive fraction and structure information such as the SMILES code.

Pre-treatment of chemical compounds [34]

The number of compounds collected from medicinal plants is very high; however, the majority lack pharmacological potency. To enhance the efficiency of screening, the first step is to remove these non-potential compounds and refine the included compounds.

Methodology [35]

Biological databases like PubChem, Drug Bank, PDB (Protein Data Bank) and software’s like Arguslab and Chemdraw. The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971(The Protein Data Bank, 2000). It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc. Arguslab offers quite good on-screen molecule-building facilities, with a moderate library of useful molecules. It is a free molecular modeling package that runs under Windows [36].

Types of software for use in computational studies [37]

Ligand based screening programs

Pre-requisite(s) for use: knowledge of compounds with known activity; use: to identify putatively active compounds; tools available: classification/ regression trees (including Random Forest), linear discriminant analysis, artificial neural
networks, and support vector machines.

**Pharmacophore programs** – Can be either ligand-based (LB), or target-based (TB) (the latter being superior/preferable); prerequisite(s) for use: 3D structures of known ligands to chosen targets (LB), or known 3D structures of target protein(s), and ideally known 3D structure(s) of known complex(es) (TB); use: to identify putative active compounds; programs available: Ligand Scout [38], Schrödinger’s Phase program [39] and Accelrys’s Discovery Studio® Catalyst.

**Docking programs**: Pre-requisites for use: known 3D structure(s) of target proteins; use: to ‘dock’ potential small molecule ligands into protein active sites, optimising their topographical and chemical complementarity, and scoring their interaction. Programs available: FlexX [40], Gold [41], Dock [42], Glide [43], Mol Dock [44], Auto Dock [45] and Ligand Fit [46].

**Other relevant types of software tool were identified as:**

**Pattern recognition software**: Use: post-screening analyses (involving dimensionality reduction); algorithms employed: principle components analysis, multi-dimensional scaling, self organising maps, and various forms of cluster analysis.

**Proteomics and/or genomics data visualization and analysis tools**: Use: application specific programs for statistical processing and visualization of data output from DNA micro-array experiments, MS proteomics experiments, etc.

**Prediction of drug like properties**

Drug-like characteristics are a qualitative concept used in drug design for a compound’s utility with respect to factors such as bioavailability, which is estimated based on the molecular structure characteristics [47]. Certain structure properties indicate that a compound has a higher likelihood of becoming a successful drug. In the past, research on these properties of a drug has been among the most important components of downstream drug development. In recent years, it has become imperative to integrate the study of drug properties during the early stages of drug discovery. Pharmacologists are interested in the following properties of the drugs, among others: (1) structural characteristics: hydrogen bonding, polar surface area, lipophiliccy, shape, molecular weight, and acid dissociation constant (pKa); (2) physicochemical properties: solubility, pH value, permeability and chemical stability; (3) biochemical properties: metabolism, protein binding affinity and transport ability; and (4) pharmacokinetics and toxicity: half-life, bioavailability, drug interactions and half lethal dose, LD50. According to Lipinski’s proposal [48], a small molecule suitable for development as a drug needs the following properties (Lipinski’s rule of five, ROS5): (1) no more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds); (2) no more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms); (3) a molecular mass less than 500 Daltons; and (4) an octanol–water partition coefficient logP not greater than (5) Small molecules that satisfy the ROS5 criteria have higher bioavailability in the metabolic process of the organism and therefore are more likely to become oral medications.

**ADME/T selection**

When drug-likeness established from the analyses of the physiochemical properties and structural features of existing drug candidates, the ADME/T (absorption, distribution, metabolism, excretion and toxicity) properties play an important role in the drug filtering. So, we employed the ADME/T selection after other drug-likeness properties evaluated [49-51].

**Successful applications in cancer drug discovery** [52-55]

The development of new anticancer drugs proves to be a very elaborate, costly and time-consuming process. CADD is becoming increasingly important, given the advantage that much less investment in technology, resources, and time are required. Due to the dramatic increase of information available on genomics, small molecules, and protein structures, computational tools are now being integrated at almost every stage of the drug discovery and development. Given the 3D structure of a target molecule, chemical compounds may have a potentially higher affinity for their target when are designed rationally with the aid of computational methods. In recent years, several cases of successful applications of structure-based drug design have been reported.

The evolution of faster advances in the enormously expanding plant sciences and natural products chemistry discipline demands high-end technological advancements in computational methods, data mining and data management. The envisioned leads, drug discovery and development, diversity in the broader natural products chemistry towards understanding of the complete influence and impact on the interdisciplinary sciences, broader subject area’s structural, functional and various other applications in several domains including medicine and veterinary medicine needs better handling of informational repository, data mining, retrieval as well as the safety, proper, benevolent and beneficial handling of the generated data. The impact of chemical understandings in various inter-linked sciences is setting new goals for challenges in bio-computing and computational resource management. The immense help from the contributions of natural products chemistry and natural products chemists have started playing its part. The prediction strategies and tools for various natural resources interactions for its probable pathways, products, biomechanics properties, software development, and other advancements in computation methods hold enormous promise for the future.

Scopoletin is constituent in *Artemisia annua* L. Scopoletin [56] might serve as the lead compound for drug development. A study on herbal lead compounds in *57* Prostate Cancer. Another study on [58] Danshen for its anti-cancer effects. Roots of *Rheum undulatum* have having components that are [59] antheraquione and stilbene derivatives, such as emodin, aloe-emodin, resveratrol, ranphtocin, and isoarrhopin and demonstrate sEH inhibitory, antibacterial, antioxidant, anticancer, and anti-inflammatory activity. *Psoralea corylifolia* plant is used for its anti-tumor effects [60]. Major components in seed is psoralidin. This study Discover novel lead for non-small cell lung cancer. This study suggests the triptolide in Cancer treatment [61]. Another study on liver tumor treated by Fuzheng Yiliu decoction. 11 constituents, showed better anticancer activity towards the cell of HepG2 cancer [62]. The X-linked inhibitor of apoptosis as a new molecular target for anticancer drugs used to resist the cancer cells to chemo and radiation therapy [63]. Phytochemical
studies on active anti-colorectal cancer compounds Alkanna tinctoria and isolated eight quinone compounds. Among that alkalnin, angelyl alkalnin, 5-methoxyangenyalkannin compounds show strong antiproliferative effects.

Table 1: Selected inhibitors developed with computational chemistry and rational drug design strategies

| Compound Name | Therapeutic Area | Function | Approvals | References |
|---------------|------------------|----------|-----------|------------|
| Imatinib      | Chronic myeloid leukemia | Tyrosine kinase inhibitor | 1990 | Buchdunger et al. (1996) [65] Druker et al. (1996) [66] |
| Gefitinib     | NSCLC            | EGFR kinase inhibitor | 2003 | Baselga et al. (2000) [67] Sirotnak et al. (2002) [68] |
| Erlotinib     | NSCLC, Pancreatic cancer | EGFR kinase inhibitor | 2005 | Pollack et al. (1999) [69] Ng et al. (2002) [70] Bulgaru et al. (2003) [71] |
| Sorafenib     | Renal cancer, Liver cancer, Thyroid cancer | VEGFR kinase inhibitor | 2005 | Heim et al. (2003) [72] Ahmad and Eisen (2004) [73] |
| Lapatinib     | ERBB2-positive breast cancer | EGFR/ERBB2 inhibitor | 2007 | Xia et al. (2004) [74] Wood et al. (2004) [75] |
| Abiraterone   | Metastatic castration-resistant prostate cancer or hormone-refractory prostate cancer | Androgen synthesis inhibitor | 2011 | Jarman et al. (1998) [76] O’Donnell et al. (2004) [77] Jagusch et al. (2008) [78] |
| Crizotinib    | NSCLC            | ALK inhibitor | 2011 | Butynski et al. (2010) [79] Rodig et al. (2010) [80] |

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; VEGFR, vascular epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2 (also known as NEU, NGL, HER2, TKR1, CD340, HER 3, MLN 19, HER-2/neu); ALK, anaplastic lymphoma kinase.

Conclusion

In silico drug design is a powerful method, especially when used as a tool within an tools, for discovering new drug leads against important anticancer targets. After a target and a structure of that target are defined, new leads can be designed from chemical principles or chosen from a subset of small molecules that scored well when docked in silico against the anticancer target. Each year, new targets are being diagnosed, structures of those targets are being determined at an amazing rate, and our capability to capture a quantitative picture of the interactions between macromolecules and ligands is accelerating. The process of novel drug discovery and development is recognized to be very expensive and time-consuming. However, thanks to recent advances in the development of physical and chemical models to simulate bimolecular processes, together with the production of increasingly powerful computational resources, discovering and designing new drugs as anticancer drugs is an affordable task for many research institutions and laboratories today. With the required computational hardware and software, and the expertise in biochemistry, biophysics, and biology, many projects that previously demanded a significant investment in time and money can be done today by a small group of researchers in their workstations. Moreover, challenging projects not even conceivable two decades ago can be today tackled with the access to a supercomputer. The optimization of these techniques and methods occurs this way naturally in its theoretical feedback signaling system. Computational models generate useful predictions to be checked with experimental results, and biologists and physicians demand approaches that are more accurate to computational scientists.

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