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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 [6-18].

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

contrast, structure-based methods rely on targeting structural information to determine whether a new compound is likely to bind and interact with a receptor. One of the advantages of the structure-based drug design method is that no prior knowledge of active ligands is required [19]. From a drug 3D structure it is possible to design new ligands that can elicit a therapeutic effect. Therefore, structure based approaches contribute to the development of new drugs through the discovery and optimization of the initial lead compound. Currently, the combination of ligand- and structure based methods has become a common approach in virtual screening since it has been hypothesized that their integration can enhance the strengths and reduce the drawbacks of each method.

In this section, some of the most representative computational approaches used to design, optimize and develop a new drug are described. Although there are remarkable differences among them, they share a common goal: harvesting potential ligands or hits with the capability to bind to the target from an extensive database of generic small chemical compounds (Figure 1). To achieve this goal, many essential steps and decisions have to be made in order to eliminate from irrelevant compounds at the beginning, to end up with those that show better potential activity or have side effects and show interaction with other drugs. This process performed with the assistance of computational algorithms is called virtual screening.

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes [20]. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively, which will be discussed in the theory section.

Knowing the location of the binding site before docking processes significantly increases the docking efficiency. In many cases, the binding site is indeed known before docking ligands into it. Also, one can obtain information about the sites by comparison of the target protein with a family of proteins sharing a similar function or with proteins co-crystallized with other ligands. In the absence of knowledge about the binding sites, cavity detection programs or online servers, e.g. GRID [21-22], 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 site 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, lipophilicity, 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, RO5): (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 RO5 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. CADDD 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 minning 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 resources 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* has having components that are [59] anthraquinone and stilbene derivatives, such as emodin, aloe-emodin, resveratrol, rhaponticin, and isorhapontin 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 alkannin, angelyl alkannin, 5-methoxyangenylalkannin compounds show strong antiproliferative effects [64].

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	Butrynski *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-2, 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.

References

1. Li HJ, Jiang Y, Li P. Nat. Prod. Rep., 2006; 23:735.
2. Newman DJ, Cragg GM. J Nat. Prod. 2007; 70:461.
3. Dhawan BN. in Decade of the Brain: India/USA Research in Mental Health and Neurosciences, ed. S.H. Koslovo, M.R. Srinivasa and G.V. Coelho, National Institute of Mental Health, Rockville, MD, 1995, 197-202.
4. Rollinger JM, Schuster D, Danzl B, Schwaiger S, Markt P, Schmidtke M *et al*. Stuppner, Planta Medica, 2009; 75:195.
5. Xie L, Evangelidis T, Bourne PE. Drug discovery using chemical systems biology: weak inhibition of multiple kinases may contribute to the anti-cancer effect of nelfinavir. PLoS Comput Biol. 2011; 7:e1002037, http://dx.doi.org/10.1371/journal.pcbi.1002037
6. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004; 3:935-49.
7. Leach AR, Shoichet BK, Peishoff CE. Prediction of proteinlig and interactions. Docking and scoring: successes and gaps. J Med Chem. 2006; 49:5851-5.
8. Combs AP. Structure-based drug design of new leads for phosphatase research. IDrugs. 2007; 10:112-115.
9. Coumar MS, Leou JS, Shukla P, Wu JS, Dixit AK, Lin WH *et al*. Structure-based drug design of novel Aurora kinase A inhibitors: structural basis for potency and specificity. J Med Chem. 2009; 52:1050-62.
10. Khan A, Prakash A, Kumar D, Rawat AK, Srivastava R, Srivastava S. Virtual screening and pharmacophore studies for ftase inhibitors using Indian plant anticancer compounds database. Bioinformation. 2010; 5:62-66.
11. Bruncko M, Oost TK, Belli BA, Ding H, Joseph MK, Kunzer A *et al*. Studies leading to potent, dual inhibitors of Bcl-2 and Bcl-xL. J Med Chem. 2007; 50:641-62.
12. Macarron R, Banks MN, Bojanic D, Burns DJ, Cirovic DA, Garyantes T *et al*. Impact of high-throughput screening in biomedical research. Nat Rev Drug Discov. 2011;10:188-95, http://dx.doi.org/10.1038/nrd3368
13. Cheung KM, Matthews TP, James K, Rowlands MG, Boxall KJ, Sharp SY *et al*. The identification, synthesis, protein crystal structure and in vitro biochemical evaluation of a new 3, 4-diarylpyrazole class of Hsp90 inhibitors. Bioorg Med Chem Lett. 2005; 15:3338-43.
14. Folkes AJ, Ahmadi K, Alderton WK, Alix S, Baker SJ, Box G *et al*. The identification of 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-ylthieno[3,2-d] pyrimidine (GDC-0941) as a potent,

selective, orally bioavailable inhibitor of class I PI3 kinase for the treatment of cancer. J Med Chem. 2008; 51:5522-32.
15. Zarghi A, Kakhki S. Design, synthesis, and biological evaluation of new 2-phenyl-4H-chromen-4-one derivatives as selective cyclooxygenase-2 inhibitors. Sci Pharm. 2014; 83:15-26.
16. Kumari S, Idrees D, Mishra CB, Prakash A, Wahiduzzaman Ahmad F *et al*. Design and synthesis of a novel class of carbonic anhydrase-IX inhibitor 1-(3-(phenyl/4-fluorophenyl)-7-imino-3H-[1, 2, 3] triazolo [4, 5d] pyrimidin 6(7H)yl) urea. J Mol Graph Model. 2016; 64:101-9.
17. Zhang HQ, Gong FH, Li CG, Zhang C, Wang YJ, Xu YG, *et al*. Design and discovery of 4-anilinoquinazoline-acylamino derivatives as EGFR and VEGFR-2 dual TK inhibitors. Eur J Med Chem. 2016; 109:371-9.
18. Nokinsee D, Shank L, Lee VS, Nimmanpipug P. Estimation of inhibitory effect against tyrosinase activity through homology modeling and molecular docking. Enzyme Res. 2015; 2015:262364 http://dx.doi.org/10.1155/2015/262364
19. Kesherwani M, Gromiha MM, Fukui K, Velmurugan D. Identification of novel natural inhibitor for NorM-a multidrug and toxic compound extrusion Transporter-an insilico molecular modeling and simulation studies. J Biomol Struct Dyn, 2016, 1-20 http://dx.doi.org/10.1080/07391102.2015.1132391
20. Martin YC, Kofron JL, Traphagen LM. Do structurally similar molecules have similar biological activity? J Med Chem. 2002; 45:4350-8.
21. Mishra V, Siva-Prasad CV. Ligand based virtual screening to find novel inhibitors against plant toxin Ricin by using the ZINC database. Bioinformation. 2011; 7:46-51.
22. Kolb P, Ferreira RS, Irwin JJ, Shoichet BK. Docking and chemoinformatic screens for new ligands and targets. Curr Opin Biotechnol. 2009; 20:429-436.
23. McConkey BJ, Sobolev V, Edelman M. The performance of current methods in ligand-protein docking. Current Science. 2002; 83:845-855.
24. Goodford PJ. A computational procedure for determining energetically favorable binding sites on biologically important macromolecules. J Med Chem. 1985; 28(7):849-857. [PubMed: 3892003]
25. Kastenholz MA, Pastor M, Cruciani G, Haaksma EE, Fox T. GRID/CPCA: a new computational tool to design selective ligands. J Med Chem. 2000; 43(16):3033-3044. [PubMed: 10956211]
26. Levitt DG, Banaszak LJ. POCKET: a computer graphics method for identifying and displaying protein cavities and their surrounding amino acids. J Mol Graph. 1992; 10(4):229-234. [PubMed:1476996]
27. Laskowski RA. SURFNET: a program for visualizing molecular surfaces, cavities, and intermolecular interactions. J Mol Graph. 1995; 13(5):323-330. 307-328. [PubMed: 8603061]
28. Glaser F, Morris RJ, Najmanovich RJ, Laskowski RA, Thornton JM. A method for localizing ligand binding pockets in protein structures. Proteins. 2006; 62(2):479-488. [PubMed: 16304646]
29. Brady GP Jr. Stouten PF. Fast prediction and visualization of protein binding pockets with PASS. J Comput Aided Mol Des. 2000; 14(4):383-401. [PubMed: 10815774]
30. Mezei M. A new method for mapping macromolecular topography. J Mol Graph Model. 2003; 21(5):463-472. [PubMed: 12543141]
31. Arlington S. An industrial revolution in R&D. Pharmaceutical Executive. 2000; 20:74-84.
32. Mandal S, Moudgil M, Mandal S. Rational drug design. European Journal of Pharmacology. 2009; 625:90-100.
33. Markus H, Seifert J, Bernd K. Virtual high-throughput screening of molecular databases. Journal of Current Opinion in Drug Discovery and Development. 2007; 10:298-307.
34. Fan Yi, Li Li, Li‐jia Xu, Hong Meng, Yin‐mao Dong, Hai‐bo Liu *et al*. In silico approach in reveal traditional medicine plants pharmacological material basis, Chin Med 2018; 13:33, https://doi.org/10.1186/s13020-018-0190-0
35. Barlow DJ, Buriani A, Ehrman T, Bosisio E, Eberini I, Hylands PJ. In-silico studies in Chinese herbal medicines' research: Evaluation of in-silico methodologies and phytochemical data sources, and a review of research to date, Journal of Ethnopharmacology. 2012; 140:526-534
36. Thomsen R, Christensen MH. MolDock: a new technique for high-accuracy molecular docking. Journal of Medicinal Chemistry. 2006; 49:3315-3321.
37. Ehrman TM, Barlow DJ, Hylands PJ. Phytochemical informatics & virtual screening of herbs used in Chinese medicine. Current Pharmaceutical Design 2010b; 16:1785-1798.
38. Wolber G, Langer T. LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. Journal of Chemical Information & Modeling. 2005; 45:160-169
39. Dixon SL, Smondyrev AM, Rao SN. PHASE: a novel approach to pharmacophore modeling and 3D database searching. Chemical Biology & Drug Design. 2006; 67:370-372.
40. Rarey M, Wefing S, Lengauer T. Placement of medium-sized molecular fragments in active sites of proteins. Journal of Computer-aided Molecular Design. 1996; 10:41-54.
41. Jones G, Willett P, Glen RC, Leach AR, Taylor R. Development and validation of a genetic algorithm for flexible docking. Journal of Molecular Biology. 1997; 267:727-748.
42. Shoichet BK, Kuntz ID. Matching chemistry and shape in molecular docking. Protein Engineering. 1993; 6:723-732.
43. Halgren TA, Murphy RB, Friesner RA, Beard HS, Frye LL, Pollard WT *et al*. Glide: a new approach for rapid, accurate docking and scoring: 1. Method assessment of docking accuracy. Journal of Medicinal Chemistry. 2004; 47:1739-1749.
44. Thomsen R, Christensen MH. MolDock: a new technique for high-accuracy molecular docking. Journal of Medicinal Chemistry. 2006; 49:3315-3321.
45. Goodsell DS, Morris GM, Olson AJ. Automated docking of flexible ligands: applications of Auto Dock. Journal of Molecular Recognition. 1996; 9:1-5.
46. Venkatachalam CM, Jiang X, Oldfield T, Waldman M. Ligand Fit: a novel method for the shape-directed rapid docking of ligands to protein active sites. Journal of Molecular Graphics & Modeling. 2003; 21:289-307.
47. Kerns EH, Li D. Drug-like properties: concepts, structure design and methods. Oxford: Elsevier LTD. 2008, 125-6.
48. Lipinski CA *et al*. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings1. Adv Drug Deliv Rev. 2001; 46(1-3):3-26.
49. Van De Waterbeemd H, Gifford E. ADMET in silico

modelling: towards prediction paradise? Nature reviews. Drug Discov. 2003; 2(3):192.
50. Dhiman V *et al*. Characterization of stress degradation products of amodiaquine dihydrochloride by liquid chromatography with high-resolution mass spectrometry and prediction of their properties by using ADMET predictor. J Sep Sci. 2017; 40(23):4530-40.
51. Willmann S, Lippert J, Schmitt W. From physicochemistry to absorption and distribution: predictive mechanistic modelling and computational tools. Expert Opin Drug Metab Toxicol. 2005; 1(1):159-68.
52. Lopez SN, Ramallo IA, Sierra MG, Zacchino SA, Furlan RLE. Chemically engineered extracts as an alternative source of bioactive natural product-like compounds, Prod. Nat. Acad. Sci. USA, 2007; 104:441-444
53. Nakamura Y, Afendi FM, Parvin AK, Ono N, Tanaka K, Hirai Morita A *et al*. KNApSAcK Metabolite Activity Database for retrieving the relationships between metabolites and biological activities, Plant Cell Physiol, 2014; 55(7), 10.1093/pcp/pct176
54. Huang Q, Qiao X, Xu X. Potential synergism and inhibitors to multiple target enzymes of Xuefu Zhuyu Decoction in cardiac disease therapeutics: a computational approach, Bioorg. Med. Chem. Lett. 2007; 17:1779-1783
55. Riaz A Khan. Natural products chemistry: The emerging trends and prospective goals, Saudi Pharmaceutical Journal, 2018; 26(5):739-753 https://doi.org/10.1016/j.jsps.2018.02.015
56. Seo EJ, Saeed M, Law BYK *et al*. Pharmacogenomics of Scopoletin in Tumor Cells. Molecules. 2016; 21(4):496. doi:10.3390/molecules21040496
57. Jayadeepa RM, Sharma S. Computational models for 5αR inhibitors for treatment of prostate cancer: review of previous works and screening of natural inhibitors of 5αR2. Curr Comput Aided Drug Des. 2011; 7(4):231-237. http://www.ncbi.nlm.nih.gov/pubmed/22050680. Accessed January 19, 2018.
58. Zhou X, Wang Y, Hu T *et al*. Enzyme kinetic and molecular docking studies for the inhibitions of miltirone on major human cytochrome P450 isozymes. Phytomedicine. 2013; 20(3-4):367-374. doi:10.1016/j.phymed.2012.09.021
59. Jo AR, Kim JH, Yan X-T, Yang SY, Kim YH. Soluble epoxide hydrolase inhibitory components from Rheum undulatum and in silico approach. J Enzyme Inhib Med Chem. 2016; 31(sup2):70-78. doi:10.1080/14756366.2016.1189421
60. Shi X, Zhang G, Mackie B, Yang S, Wang J, Shan L. Comparison of the in vitro metabolism of psoralidin among different species and characterization of its inhibitory effect against UDP- glucuronosyltransferase (UGT) or cytochrome p450 (CYP450) enzymes. J Chromatogr B 2016; 1029-1030:145-156. doi:10.1016/j.jchromb.2016.06.031
61. Zhao GF, Huang ZA, Du XK, Yang ML, Huang DD, Zhang S. Molecular docking studies of Traditional Chinese Medicinal compounds against known protein targets to treat non-small cell lung carcinomas. Mol Med Rep. 2016; 14(2):1132-1138. doi:10.3892/mmr.2016.5350
62. Chen L, Du J, Dai Q, Zhang H, Pang W, Hu J. Prediction of anti-tumor chemical probes of a traditional Chinese medicine formula by HPLC fingerprinting combined with molecular docking. Eur J Med Chem. 2014; 83:294-306. doi:10.1016/j.ejmech.2014.06.037
63. Nikolovska-Coleska Z, Xu L, Hu Z *et al*. Discovery of embelin as a cell-permeable, small-molecular weight inhibitor of XIAP through structure-based computational screening of a traditional herbal medicine three-dimensional structure database. J Med Chem 2004; 47(10):2430-2440. doi:10.1021/jm030420+
64. Tung NH, Du GJ, Yuan CS, Shoyama Y, Wang CZ. Isolation and chemopreventive evaluation of novel naphthoquinone compounds from Alkanna tinctoria. Anticancer Drugs. 2013; 24(10):1058-1068. doi:10.1097/CAD.0000000000000017
65. Buchdunger E, Zimmermann J, Mett H, Meyer T, Müller M, Druker BJ *et al*. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. Cancer Res. 1996; 56:100-104.
66. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, *et al*. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. 1996; 2:561-566.
67. Baselga J, Averbuch SD. ZD1839 (‘Iressa’) as an anticancer agent. Drugs. 2000; 60 Suppl 1:33-40.
68. Sirotnak FM, Zakowski MF, Miller VA, Scher HI, Kris MG. Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. Clin Cancer Res. 2000; 6:4885-92.
69. Pollack VA, Savage DM, Baker DA, Tsaparikos KE, Sloan DE, Moyer JD *et al*. Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358,774: dynamics of receptor inhibition in situ and antitumor effects in athymic mice. J Pharmacol Exp Ther. 1999; 291:739-48.
70. Ng SS, Tsao MS, Nicklee T, Hedley DW. Effects of the epidermal growth factor receptor inhibitor OSI-774, Tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Mol Cancer Ther. 2002; 1:777-83.
71. Bulgaru AM, Mani S, Goel S, Perez-Soler R. Erlotinib (Tarceva): a promising drug targeting epidermal growth factor receptor tyrosine kinase. Expert Rev Anticancer Ther. 2003; 3:269-79.
72. Xia W, Liu LH, Ho P, Spector NL. Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. Oncogene. 2004; 23:646-53.
73. Wood ER, Truesdale AT, McDonald OB, Yuan D, Hassell A, Dickerson SH *et al*. A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. Cancer Res. 2004; 64:6652-9.
74. Heim M, Sharifi M, Hilger RA, Scheulen ME, Seeber S, Strumberg D. Antitumor effect and potentiation or reduction in cytotoxic drug activity in human colon carcinoma cells by the Raf kinase inhibitor (RKI) BAY 43-9006. Int J Clin Pharmacol Ther. 2003; 41:616-7.
75. Ahmad T, Eisen T. Kinase inhibition with BAY 43-9006 in renal cell carcinoma. Clin Cancer Res. 2004; 10 18 Pt 2:6388S-92S.
76. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H *et al*. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004; 64:7099-109.

77. Jarman M, Barrie SE, Llera JM. The 16, 17-double bond is needed for irreversible inhibition of human cytochrome p45017alpha by abiraterone (17-(3-pyridyl)androsta-5, 16-dien-3beta-ol) and related steroidal inhibitors. J Med Chem. 1998; 41:5375-81.
78. O'Donnell A, Judson I, Dowsett M, Raynaud F, Dearnaley D, Mason M *et al*. Hormonal impact of the 17alphahydroxylase/ C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer. 2004; 90:2317-25.
79. Jagusch C, Negri M, Hille UE, Hu Q, Bartels M, Jahn-Hoffmann K *et al*. Synthesis, biological evaluation and molecular modeling studies of methyleneimidazole substituted biaryls as inhibitors of human 17alpha-hydroxylase-17, 20-lyase (CYP17). Part I: Heterocyclic modifications of the core structure. Bioorg Med Chem. 2008; 16:1992-2010.
80. Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC *et al*. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med. 2010; 363:1727-33.
81. Rodig SJ, Shapiro GI. Crizotinib, a small-molecule dual inhibitor of the c-Met and ALK receptor tyrosine kinases. Curr Opin Investig Drugs. 2010; 11:1477-90.