WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

NETWORK PHARMACOLOGY : A New Avenue For Drug Development

Akash Jain, Huzaif Mohd. Khan, Jitendrasingh Rampure, Kartavya Bairagi, Krishna Kumar

Student of B.Pharm 4th Year

Dr. Abhishek Pandey, Dr. Sunisha Kulkarni, Mr.Rajendra Chauhan

Counsellor and Guider

Dr. Suman Jain

HOD OF S.O.S. in Pharmaceutical Science College Jiwaji University Gwalior

ABSTRACT

The development of new drug is not only the main driving force for the development of pharmaceutical industry, but also plays a very important role in the social development. However, with the increasing demands, new drug development is facing great difficulties in recent years. The hypothesis of highly selective single-target is meeting the challenges because of its limitations. Network pharmacology has been one of the new strategies for new drug discoverybased on single-target drug research in recent years. This paper focused on the basis of network pharmacology and its research progress, discussed its development direction and application prospects, and analyzed its limitations and problems as well. The application of network pharmacology in new drug development is discussed by comparing its guidelines with those of traditional Chinese medicine theory and Effective Components Group hypothesis of Chinesemedicines.

KEYWORDS : : Network pharmacology, multi-target virtual screening, drug- target interaction, chemical-protein interactome, traditional chinese medicine, side effect similarity

1. INTRODUCTION

Drug discovery, the process by which new candidate medications are discovered, initially began with random searching of therapeutic agents from plants, animals, and naturally occurring minerals . For this, they depended on the material medica that was established by medicine men and priests from that era. This was followed by the origin of classical pharmacology in which the desirable therapeutic effects of small molecules were tested on intact cells or whole organisms. Later, the advent of human genome sequencing revolutionizedthe drug discovery process that developed into target based drug discovery, also known as reverse pharmacology[1]. This relies on the hypothesis that the modulation of the activity of a specific protein will have therapeutic effects. The protein that the drug binds to or interacts with is also referred to as a "target." In this reductionist approach, small molecules from a chemical library are screened for their effect on the target's known or predicted function. Oncethe small molecule is selected for a particular target, further modifications are carried out at the atomic level to ameliorate the lock-and-key interactions. This one-drug/one target/one- therapeutic approach was followed for the last several decades. The information technology revolution at the end of 20th century metamorphosed the drug discovery process as well. Advancements in omics technologies during this time were used to develop strategies for different phases of drug research. Computational power was implemented in the discovery process for predicting a drug-likeness of newly designed or discovered compounds and ligand protein docking for predicting the binding affinity of a small molecule with a protein three- dimensional structure. In silico tools were developed to predict other pharmacological properties of the drug molecules such as absorption, distribution, metabolism, excretion, and toxicity—abbreviated together as ADMET. The technological advancements triggered discovery efforts in a direction to discover more specific magic bullets that were completely against the holistic approach of traditional medicine. This magic bullet approach is currently in decline phase. The major limitations of this drug discovery approach are side effects and theinability to tackle multifactorial diseases. This is mainly due to the linearity of this approach.

During the peak, historical time of drug discovery and development of natural products based drugs had played a significant role due to their superior chemical diversity and safety over synthetic compound libraries . Currently, it is estimated that more than one hundred new, natural product based leads are in clinical development. Many active compounds (bio actives) from traditional medicine sources could serve as good starting compounds and scaffolds for rational drug design. Natural products normally act through modulation of multiple targets rather than a single, highly specific target. But in drug discovery and development, technology was used to synthesize highly specific mono-targeted molecules that mimic the bio actives from natural

compounds rather than understanding the rationale behind their synergistic action and developing methods to isolate the bio actives from natural resources. Researchers understand that most diseases are due to dysfunction of multiple proteins. Thus, it is important to address multiple targets emanating from a syndrome-related, metabolic cascade, so that holistic management can be effectively achieved. Therefore, it is necessary to shift the strategy from one that focuses on a single-target, new chemical entity to one of a multiple-target, synergistic, formulation-discovery approach . This tempted the research world to go back and extensively explore natural sources, where modern pharmacology had begun. This renewed research focus indicates the need to rediscover the drug discovery process by integrating traditional knowledge with state-of-the-art technologies .[2]

2.NETWORK PHARMACOLOGY

A new discipline called network pharmacology (NP) has emerged which attempts to understand drug actions and interactions with multiple targets. It uses computational power to systematically catalogue the molecular interactions of a drug molecule in a living cell. NP appeared as an important tool in understanding the underlying complex relationships between botanical formula and the whole body. It also attempts to discover new drug leads and targets and to repurpose existing drug molecules for different therapeutic conditions by allowing an unbiased investigation of potential target spaces. However, these efforts require some guidance for selecting the right type of targets and new scaffolds of drug molecules. Traditional knowledge can play a vital role in this process of formulation discovery and repurposing existing drugs. By combining advances in systems biology and NP, it might be possible to rationally design the next generation of promiscuous drugs. NP analysis not only opens up new therapeutic options, but it also aims to improve the safety and efficacy of existingmedications.[3]

02 Concept and Significance of Network Pharmacology

The efforts of molecular biology and genomics research have provided large data which helped in gaining new insights into drug discovery processes. Hopkin, the father of Network Pharmacology, explained that a single drug can target multiple nodes in the disease network [4]. Network pharmacology is based on the integration of multiple disciplinary concepts including molecular biology, biochemical biology and bioinformatics [4-5]. Network pharmacology has gained more interest due to high success rate in clinical investigation, less or affordable side effects, enhanced drug efficacy, regulation of the signaling pathway with multiple channels, interaction of multiple genes and proteins that could be easily be targeted causing the disease [6]. In addition, network pharmacology also helps in finding the disease node which is an important disease node. Beside these, it also increases the clinical candidates with potency and reduces the attrition rate in the disease network [7]. Around 40% of the current drug discoveries are contributed by network pharmacology rather than a magic bullet philosophy [6, 7].

3.RESEARCH APPROACHES AND AVAILABLE DATABASERESOURCES

A newly emerged area in the field of drug discovery is network pharmacology which uses mainly two approaches, establishing a network and utilization of public databases. Prediction of drug target disease network using HTS technology in combination with bioinformatics is among the other approaches in this area . In the area of network pharmacology, the approaches could be divided into computational and experimental approaches. The computational approaches mainly include graph theory, statistical methods, data mining, modeling, and information visualization methods. The experimental approaches include various high throughput omics technologies and biological and pharmacological experiments. In network 2pharmacology, some common steps include data sources, big data analytics, network construction, interactions prediction and network analysis [8]

3.1. *Data source*

Experimental verification and public databases are the two main sources of data collection innetwork pharmacology. By utilizing the existing research and available data, a target can be identified for the drug followed by an experimental validation. Another approach to collect data is omics technology [8]. The available databases and resources are summarized below.

3.1.1. Drug Bank

The Drug Bank database is an abundantly interpreted bioinformatics and cheminformatics resource. Drug Bank combines multi array information regarding the drug candidates. This information largely comes from pharmaceutical, chemical and pharmacological sources along with target information. Statistics of this database reported 7759 drug entities till now and 15,199 drug–target interactions.[8]

3.1.2. TTD: Therapeutic Target Database

Therapeutic Target Database (TTD) provides the information about some known and different aspects of a disease. This information largely includes proteins which are therapeutically significant, nucleic acid (DNA & RNA) targets, disease specific characterization, pathway information and consistent drugs acting on different targets. Like other databases, TTD also holds 1755 biomarkers for about 365 disorders and 210 scaffolds. These 210 scaffolds are of around 714 drugs. TTD is also enriched with a variety of lead compounds. Targets and drugs included in TTD are of great clinical importance, under use and trials. These targets and drugs are found to be very useful in accelerating the process of modern in silico drug discovery and experiments.[9]

3.1.3. Matador

To obtain the information regarding multiple direct and indirect modes of drug–target interactions and protein– chemical interactions,

Manually Annotated Targets and Drugs OnlineResource (MATADOR) is a frequently accessed database. Direct and indirect binding of proteins and chemicals could be accessed by searching a drug or a protein . [10]

3.2. Data source

Experimental verification and public databases are the two main sources of data collection in network pharmacology. By utilizing the existing research and available data, a target can be identified for the drug followed by an experimental validation. Another approach to collect data is omics technology [8]. The available databases and resources are summarized below.

3.2.1. Drug Bank

The Drug Bank database is an abundantly interpreted bioinformatics and cheminformatics resource. Drug Bank combines multi array information regarding the drug candidates. This information largely comes from pharmaceutical, chemical and pharmacological sources along with target information. Statistics of this database reported 7759 drug entities till now and 15,199 drug–target interactions.[8]

3.2.2. TTD: Therapeutic Target Database

Therapeutic Target Database (TTD) provides the information about some known and different aspects of a disease. This information largely includes proteins which are therapeutically significant, nucleic acid (DNA & RNA) targets, disease specific characterization, pathway information and consistent drugs acting on different targets. Like other databases, TTD also holds 1755 biomarkers for about 365 disorders and 210 scaffolds. These 210 scaffolds are of around 714 drugs. TTD is also enriched with a variety of lead compounds. Targets and drugs included in TTD are of great clinical importance, under use and trials. These targets and drugs are found to be very useful in accelerating the process of modern in silico drug discovery and experiments.[9]

3.2.3. Matador

To obtain the information regarding multiple direct and indirect modes of drug–target interactions and protein– chemical interactions, Manually Annotated Targets and Drugs OnlineResource (MATADOR) is a frequently accessed database. Direct and indirect binding of proteins and chemicals could be accessed by searching a drug or a protein . [10]

3.2.4. Integrity

This database covers a large number of clinical drug candidates corresponding to their drug targets, diseases and the statistics on clinical phases of the drugs.[16]

3.2.5. FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information obtained from an adverse event and medication error reports submitted to FDA on side effect keywords (adverse event keywords) for drugs. [17]

3.2.6. Sider

SIDER database collects information regarding the side effects (i-e frequency) of already approved drug candidates. Classifications, linking to further information such as drug– target associations, are also one of the major aims. [18]

3.2.7. JAPIC

Japan Pharmaceutical Information Center (JAPIC) covers the information regarding pharmaceutical circle in Japan. Information such as side effects for drugs (pharmaceutical molecules) is mainly added.[19]

3.2.8. Chem Bank

Chem Bank is a freely accessed database resourced with information about small molecules so that insights can be gained. Chem Bank is unique among small-molecule databases in the following three ways: its holds a large space for raw screening data storage, having rigorous definition of screening experiments in terms of statistical hypothesis testing and hierarchical metadata-based organization of related assays into screening projects.[20]

3.2.9. Cancer DR

The Cancer DR offers information of 148 anti-cancerous agents, and their pharmacological profiling across 952 cancer cell lines. Comprehensive information, such as 1356 unique mutations, gene ontology, pathways, and phylogeny about the drug targets, is available in this database. The design of an effective and personalized cancer treatment and the identification of genes encoding drug targets could be easily mapped from this database.[21]

3.2.10. Binding DB

Binding DB is a public, web-accessible database of measured binding affinities, focusing chiefly on the interactions of protein considered to be drug-targets with small, drug-like molecules. As of May 4, 2022, Binding DB contains 41,296 Entries, each with a DOI, containing 2,513,948 binding data for 8,839 protein targets and 1,077,922 small molecules.[22]

3.2.11. Zinc

ZINC is the largest database for ligand discovery, especially investigating novel drug candidates for biological targets. ZINC contains >20 million commercially available compounds for ligand discovery and virtual screening. [23]

3.2.12. Cansar

Cansar is a cancer research database information about biological data (annotations of biological data, screening of RNA interference and chemical agents, expression and 3D structural). The integration of this diverse data set aids in cancer research and discovery of drugcandidates for the treatment of various cancers.[24]

3.2.13. ASDCD

DCDB is a database which holds information of antifungal drug research in order to help in drug combination analysis and new antifungal drug development. To date, 210 antifungal drug combinations and 1225 drug–target interactions involving 105 individual drugs from >12 000references have been resourced. [25]

3.2.14. Dinies

Drug–target interaction network inference engine is based on a supervised analysis. DINIES, is a web server to infer potential drug–target interaction network. DINIES can accept flexible input data, such as chemical structure, side effects, amino acid and protein domains. Furthermore, each data set can be transformed into a kernel similarity, and various state-of-the-art machine learning methods are used to realize the drug–target interactions prediction.[26]

3.2.15. Super Pred

Anatomical Therapeutic Chemical (ATC) code and drugs targets are predicted by the online server Super Pred. For ATC code prediction, different criteria such as pipeline search could be used for the integration of 3D, 2D and frag The Binding DB has information about 1,132,739 experimentally measured protein-ligand binding affinities. Among these, 4,894,16 are small molecule such as ligands while 7020 (receptors) are protein targets. It has become one of the most extensive public databases of protein–ligand binding affinities. ment similarity. Drug target prediction is based on the similarity distribution, which can estimate individual thresholds and probabilities for a specific target by four input options. [27]

3.2.16. Swiss Target Prediction

Swiss Target Prediction is a web server to deduce the targets of bioactive small compounds based on the combination of 2D and 3D similarity values with the known ligands. Five different organisms, including Homo sapiens, Mus musculus, Rattus norvegicus, Bos taurus and Equuscaballus can be inquired using Swiss Target Prediction.[28]

3.3. Big Data Analytics

For large and complex networks, the traditional approaches may not be sufficient to fully understand the disease network. Therefore, highly analytical techniques such as high- performance data mining, predictive analytics, text

mining, forecasting and optimization are required to unveil the hidden information. In addition, machine learning could be useful to addressing other needs [29,30]].

3.4. Network Construction and Interactions Prediction

Understanding the network of the disease is the most important step of the network pharmacology. How to construct a network disease is another complicated aspect of this analysis but certain approaches have been made to understand and exploit it for new drug candidates [31]. Some known approaches are: gene locality [32], phylogenetic reconstruction [31], fusion of genes [33], correlated evolutionary rate [34], mirror tree [33], correlated mutations [35], homologous structural complexes [36] and prediction from primary structure [37]. Network construction and their interaction can be significantly done by using phylogenetic profiling. Node-based network mapping and as well as correlation-based is considered as the promising for future discoveries [38].

3.5. Network Analysis

Network is a well-computed mathematical representation of various connected nodes and edges. A major portion of the network pharmacology is network analysis which mainly covers attribute analysis, topological analysis, network structure and stability, flow (flux) balance analysis and network models. A network analysis usually measures module, betweenness, hub, node, edge, shortest path and degree of hub gene. Fig. (1) shows the topological parameters ofa network. [38]

- Module: A group of nodes that act in concert to perform a specific function.
- Hub: A node with high degree.
- Degree: the number of edges connected to a node.
- Betweenness: the number of shortest paths that go through a given specific node.
- Shortest path: A minimum path between any two nodes in a network
-

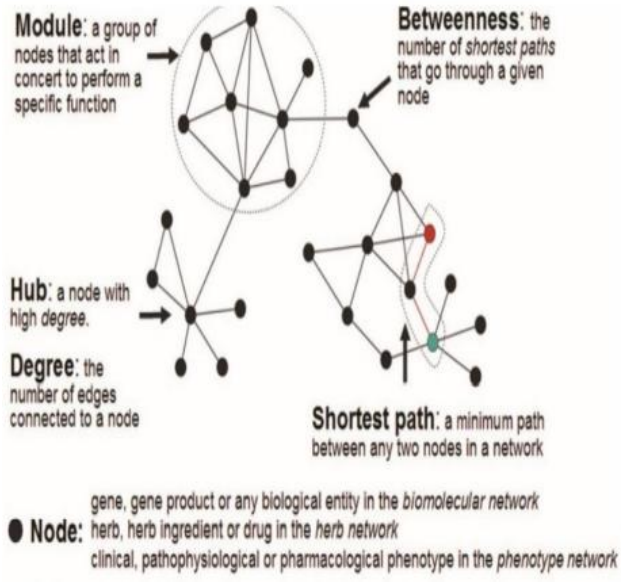


Fig : (1) – The figure is describing a topology of a network . It includes modules, Between ,Hub , node, edge , shortest path and degree of hub gene .

3.5 *Methods in Network Pharmacology*

3.5.1. Identification of Drug Target Interaction

In genomic drug discovery, the identification of drug target interaction is considered as a key area of interest. The interactions of small molecules with different pharmaceutically important protein targets modulate its activity. The application of various biological assays for the high throughput screening of large chemical databases enabled the identification of drugs with different targets [39,40,41]. Chemical genomic research aimed to relate the chemical spaces with genomic spaces, however, the relationship of chemical and genomic is very limited. For example, the PubChem database has information about millions of compounds but information about the interactions with their targets is very limited [42]. The experimental determination of compound protein interactions or potential drug–target interactions is time-consuming and cost-effective [43,44]. So, an effective in silico prediction method needs to be developed.

3.5.2. Prediction of Drug-target Interaction Networks Via Chemical and Genomic Spaces

In 2008 Yaminishi proposed three methods based on chemical and genomics spaces [45]. They obtained the drug target interactions from the Super Target, KEGG BRITE, Drug Bank databases and BRENDA [, 40,46,47]. The information about chemical data was obtained from the KEGG LIGAND database. The structure similarity was computed by the SIMCOMP methods [48]. The methods proposed are the nearest profile method, weighted profile method and bipartite graph learning method. Previously two research approaches have been used for the identification of drug-target interactions, the chemical biology and the traditional drug discovery approach. In traditional drug discovery, new lead compounds are identified for the few targets. In chemical biology, novel targets are identified for the few chemical compounds.. Among these methods, Bipartite graph learning method has the advantage to predict the interaction for previously unseen drug candidate compounds and target candidate proteins [45] while other methods, the nearest profile and weighted profile methods cannot predict the interaction for the previously unseen drug candidate compounds and target candidate proteins. The nearest profile method predicts the interaction based on the structure sequence similarity and hence may give false positive results. Because many target candidates such as enzymes share sequence similarity but bind to different chemicals. Some other methods such as docking simulation can predict the interaction but it needs three-dimensional structures of the target protein candidates [49,50]. Many of the pharmaceutically important drug targets are GPCRs and ion channels. Predicting the three dimensional structure of these proteins is a challenging

task, hence, it limits the molecular docking approach to predict the drug target interaction. The Bipartite graph learning method does not need three dimensional structures. Therefore, bipartite graph learning method has an advantage that it is suitable for screening a huge number of drug candidate compounds and target proteins at a large scale.

3.5.3. Prediction of Drug–target Interaction Networks Through Side Effect Similarity

The treatment of human disease with selected drugs results in regulated recording of side effects. These side effects are directly attributed to the interaction of drugs with primary targets and off targets (additional target) and seem to be one of the most important scenarios [51-53]. The interaction of drugs with off-target derives unexpected and harmful results. But , sometimes these interactions have a beneficial effect and lead to a new therapeutic area for drugs [54]. For example, sildenafil was used to treat angina, but its side effect in human volunteers prolonged penile erections, which led to a new therapeutic area for sildenafil [54] . Monica Campillos et al. mentioned that unrelated drugs that share similar side effects, must have common off-targets [55]. For example, the two unrelated drugs, cisapride and astemizole, bind to the cardiac ion channel hERG, thus inhibit its activity and both cause cardiac arrhythmias [56]. Monica Campillos et al. take advantage of the side effect and developed a method for the side effect similarity and analysis, the likelihood of sharing the target of marketed available drugs [55]. Through in-vitro binding assays, they confirmed experimentally that the side effect similarity of unrelated drugs indeed shares

a common protein target. Through the application of side effect similarity, Monica Campillos et al. suggest new targets for marketed drugs of different therapeutic categories (Table 1). The new targets were found experimentally to bind with drug candidates with good binding affinity. Side effects open a new dimensional space for predicting the poly pharmacology of the drug [57]. Feixiong Cheng et al. developed a database for predicting the side effects named Meta ADEDB [58]. Taking the advantage of the side effects, Feixiong Cheng et al. found the network pharmacology of the drugs and found new potential targets [59].

Table 1. Experimentally validated off-targets for the marketed drugs through side effect similarity me

Drug	**Off-target**	**Ki (μM)**
Donepezil	5HTT	9
Fluoxetine	dopamine receptor (DRD3)	2
Rabeprazole	serotonin receptor (HTR1D)	7.6
Rabeprazole	dopamine receptor (DRD3)	1.6
Paroxetine	dopamine receptor (DRD3)	3.8
Zaleplon	HRH1	26
Disopyramide	HRH1	2.7
Clomiphene	HRH1	6.5
Loratodine	BZR	5
Raloxifene	Serotonin receptor (HTR1D)	0.3
Acitretin	HRH1	15
Doxorubicin	HRH1	10
Ketoconazole	serotonin receptor (HTR1D)	2.8

3.5.4. Prediction of Drug–target Interaction Networks by Integrating the Pharmacological Space into Chemical and Genomic Spaces

The in-silico prediction of the drug target interaction from heterogeneous biological data is important to discover the drugs and target candidates for the known disease. The chemical genomics has made it possible to relate the chemical space with genomic space, but genome wide detection of drug target interaction is the key issue in chemical genomic research [39-41]. Thus, in 2010, Yamanishi proposed a new method that relates the chemical space with the pharmacological space and the integration of drug target network topology [60]. They showed that the drug–target interaction is mostly correlated with a pharmacological effect similarity than with chemical structure similarity. Owing to the proposed method, the unknown drug target interactions are predict at a large scale from the information of genomic sequence, chemical structure and pharmacological effect. The method consists of two steps: (1) inference of the pharmacological information from the structure of a given compound via an algorithm developed by Scheiber [61] (2) prediction of the interaction between drug and target based on

the pharmacological effect similarity in the supervision of bipartite graph inference [45, 62]. In fact, the proposed method here is the extension of the work by Yamanishi .[45]. The performance of the proposed methods was evaluated for the four different classes of proteins to reconstruct the drug target interaction in terms of three inputs (i) similarity of the chemical structure (ii) true pharmacological similarity, and (iii) predicted pharmacological similarity. The four different classes include ion channels, enzymes, nuclear receptors and GPCRs. The statistics of the proposed method is summarized in Table 4. In Table 4, the input, and chemical structure similarity are based on the previous method [45] while the input, and true pharmacological similarity and predicted pharmacological similarity are based on the proposed method. The previous study in the same area uses side effect similarity, but the method is only applicable to the marketed information available of drugs with side effects [55]. Thus, the method proposed by Yamanishi in 2010 is able to predict the pharmacological information about not only the marketed drugs but also any drug candidate.

3.5.5. Prediction of Drug–target Interaction Via Chemical protein Interactome (CPI)

Approximately 90 percent of the drug candidates fail during the different developing phases before launching into the market. It makes the research and developing process extremely expensive and time-consuming. The identification of novel indication for the already available marketed drug might lower the research and development costs [54, 63]. The de novo development of a drug takes approximately 10-17 years with regulatory, efficacy and quality risk. The repurposing of the drugs has the advantage of decreased research and developing cost with launching time due to the previously collected pharmacokinetic, toxicology and safety data. The adverse side effects of the drug have been known as the leading cause of death of hospitalized patients and have been concerned word-widely [64,65].

These new indications and adverse side effects are caused by unwanted drug-protein interactions [66-71]. The prediction of this interaction is possible by mining the chemical- protein interactome (CPI) [73]. Several other techniques such as drug affinity pull-down and BIACORE biosensors can be used to predict unwanted or unexpected chemical-protein interactions [74,75] but CPI has an advantage of low cost. The first CPI released by the Lun Yang et al. contains 162 chemicals and 891 binding pockets [73]. The chemicals selected in the CPI are FDA approved drugs, each of which causes at least one of the major serious adverse drug reactions (SADRs) including deafness, cholestasis, Stevens-Johnson syndrome (SJS) and

rhabdomyolysis. As the human knowledge about SADRs is limited, the target proteins in the CPI were selected from the literature and protein targetable databases [76-79]. Through the application of CPI, Lun Yang et al. harvested the genes responsible for the SJS [73]. The CPI has the advantage of predicting the specific alleles that is more sensitive to the drug attack. HLA-B*57 has been conformed as the susceptible gene of SADRs causing hypersensitive reaction in response to abacavir [79,80]. The structure of both the risk and non-risk allele of HLA-B*57 is available [81,82]. Lun Yang . construct the CPI, containing interaction strength for the four structures of risk and non-risk allele with abacavir, allopurinol. The author found no specificity of allopurinol to any of the proteins. This result is in accordance with the fact that none of these alleles are the risk alleles for allopurinol-induced SADRs. It's clear from Table 5 that B*5703 is not the susceptible allele because abacavir cannot fit into the binding site of B*5703. While the allele B*5701is found to be the risk allele. The major difference between the two alleles lies in two polymorphisms (N114D, Y116S) from B*5703 to B*5701. Through CPI, it is deduced that B*5701 tends to be the risk allele compared to B*5703.

Taking the advantage of CPI, Heng Luo et al. introduced a web server named DRAR-CPI [83]. The server contains 385 human targetable proteins and 254 molecules with descriptions, indications and ADRs. The server accepts molecules in mol, ml2, mol2, pdb, sdf and SMILES. Dock programs implemented in the server are used to predict the binding energy of the submitted molecule and targets. The author developed an algorithm based on connectivity analytics [84] which calculate the positive or negative association scores between the submitted drug and the server molecules. The two-directional Z-transformation (2DIZ) is applied to

association scores [85]. The target having association score less than 1 is treated as a favorable target while greater

than 1 is treated as unfavorable. It can also predict the off-targets for the submitted molecule so that users can predict potential indications or ADRs based on the association scores of their molecule across our library molecules. The reliability of the server was checked by comparing the predicted drug-drug associations and drug-drug association through genee xpression profiles. The matching rate was found to be 74%. Heng Luo et al. found a new indication and ADRs for the Rosiglitazone, a drug used as an anti-diabetic through the application of DRAR-CPI server [83, 86]. Several studies have been published, using DRAR-CPI server, regarding the discovery of the new indication and ADRs for the different drugs [87-95].

Owing to the complex network-based theory [96-99], Feixiong Cheng et al. proposed the three methods named target-based similarity inference (TBSI), network-based inference (NBI) and drug-based similarity inference (DBSI) [101]. The performance of these methods is checked with four benchmark data sets. Four major drug targets were included in these data sets named as ion channels, enzymes, GPCRs, nuclear receptors and GPCRs. After several statistical analyses, the NBI method was found to be the best. Based on the NBI method, the drug target interaction of the FDA approved and experimental drug was determined. New targets were successfully predicted for the five approved drugs following the NBI method [101]. The NBI method was further improved by Feixiong Cheng et al. by weighting the edge and nodes of the CPI to achieve the better accuracy of drug target interaction [102]. In the Edge Weighted Network-based Inference (EWNBI), each edge of the CPI is weighted according to the strength of the inhibitory activity or binding affinity of chemical and protein node [102]. In Node Weighted Network-based Inference (NWNBI), a new expression of initial resource distribution of nodes is used which takes into account the influence of resources associated with the receiver nodes in the CPI bipartite network [103]. This method is based on the general knowledge that the hub node with more resources is more difficult to be influenced. These two improved methods slightly outperformed the original NBI.

Because of the lack of connections between the newly synthesized chemical or failed drugs, in phases II and III, and the existing DTI network, the aforementioned methods cannot predict the new potential targets for the known drugs unless the known target present in the existing DTI network. To overcome this pitfall, in 2016, Zengrui Wu proposed chemo informatics tool and an integrated network named substructure–drug–target network-based inference (SDTNBI) [104]. To bridge the gap between the newly synthesized structure and known drugs, SDTNBI uses a substructure which is shared by the chemical structures. The chemical substructure has a significant role in the computational evaluation of drug pharmacokinetics and DTI prediction suggested by the previous studies [105-108]. Thus, SDTNBI can prioritize potential targets for old drugs, clinically failed drugs, and new synthesized chemicals at a large scale. However, several pitfalls exist in the SDTNBI, as they cannot predict the potential DTIs for the subject targets that are absent from the existing DTIs because of lack of connection among those targets and the known network. Moreover, it cannot predict the accurate DTIs for the new chemical molecule that shares no substructure or few substructures.

Zengrui Wu have made an improvement in the original SDTNBI by introducing the three parameters [109]: (i) the initial resource allocation of different nodes (i.e. substructure nodes

and target nodes), (ii) the weighted values of different edges (i.e. drug-substructure associations and drug target interactions), and (iii) the influence of hub nodes, respectively. The improved SDTNBI was named as a balanced substructure-drug-target network-based inference (b SDTNBI). Zengrui Wu et al. found the molecular mechanism of action (MOA) of tricyclic anti- depressant agent promethazine and clomipramine via b SDTNBI [109]. Previous studies suggested that both promethazine and clomipramine induce cell apoptosis in different cancer cells but the anticancer MAA of these drugs remains unclear [110-113]. Through b SDTNBI, promethazine and clomipramine were found to target the serotonin receptors (HTR1A and HTR1D) with high score. These receptors might be involved in different cancer types. Moreover, through b SDTNBI, several antidiabetics drugs such as pioglitazone, rosiglitazone and dapagliflozin were repurposed for cancer treatment by targeting the nuclear receptors such as CA1, PPARG, RARB, and RXRA [109]. Collectively, b SDTNBI would provide a powerful tool for the identification of chemical MOA in drug discovery and development.

3.5.6. Prediction of Drug-target Interaction Through a Network-based Random Walk with Restart on the Heterogeneous Network

The drugs with similar structures often interact with similar proteins. Chen developed a model of Network based Random Walk with Restart on the Heterogeneous network (NRWRH) that effectively predicts the drug target interaction based on the above assumption and by the integration of drug-drug similarity network, protein-protein similarity network and know drug- target interaction networks into a heterogeneous network [114]. For the integration of data and drug–target interactions prediction, NRWRH makes the full use of the network tool that is different from the traditional random walk with restart. In case of NRWRH, the random walk is applied to the heterogeneous network which consists of different sub-networks such as drug chemical structure similarity network, and target protein sequence similarity network and drug–target interactions network. This method has an advantage of predicting the novel target for the subject drug which has no known target. The potential target can be predicted based onthe known targets of drugs, which are similar to given subject drug.

3.5.7. Prediction of Drug –target Interaction Through A Rotation Forest- based Predictor

Based on the hypothesis that drug target interactions are mainly determined by the primary structure of the target protein sequence and substructure fingerprints of drug molecules, Lei

Wang et al. proposed a novel method for the drug target interactions [115]. In the proposed method, the interactions of the drug with the target are predicted under the theory that each drug-target interaction pair can be represented by the structural properties of the drugs and evolutionary information derived from proteins. The biological evolutionary information of theprotein sequences is encoded as Position-Specific Scoring Matrix (PSSM) descriptor. The drug molecules are encoded as fingerprint feature vectors which represent the existence of certain functional groups. First, the protein sequence is converted into the PSSM matrix and then the auto covariance algorithm was used to extract features from PSSM containing biological evolution information to combine it with molecular substructure fingerprints information to form a feature vector. At last, the drug target interaction is predicted by a rotation forest (RF) classifier. The prediction accuracy of the proposed method was found to be 71.1%, 84.1%, 89.1% and 91.3% for four data sets' nuclear receptors, GPCRs, ion channels and enzymes, respectively. Later, in 2016, Yu-An Huang et al. proposed a model based on the same assumption of Lei Wang et al. [115,116]. Here the protein sequences were encoded by the Pseudo Substitution Matrix Representation (Pseudo SMR) descriptor due to which the influence of biological evolutionary information retained. The drug molecules were represented by the structural activity relationship (SAR). The extremely randomized trees (ETs) classifier was used instead of RF classifier to build the model for the four data sets' nuclear receptors, GPCRs, ion channels and enzymes. The prediction accuracy of the Lei Wang et al. model was 81.67%, 82.99%, 87.87% and 89.85% for the four nuclear receptors.

3.6. *Network Cunstruction*

A network is the schematic representation of the interaction among various entities called nodes. In pharmacological networks, the nodes include bioactive targets, tissue, tissue types, disease, disease types, and pathways. These nodes are connected by lines termed edges, which represent the relationship between them [80]. Building a network involves two opposite approaches: a bottom-up approach on the basis of established biological knowledge and a top- down approach starting with the statistical analysis of available data. At a more detailed level, there are several ways to build and illustrate a biological network. Perhaps the most versatile and general way is 144 Innovative Approaches in Drug Discovery the de novo assembly of a network from direct experimental or computational interactions, e.g., chemical/gene/protein screens. Networks encompassing biologically relevant nodes (genes, proteins, metabolites), their connections (biochemical and regulatory), and modules (pathways and functional units give an authentic idea of the real biological phenomena.

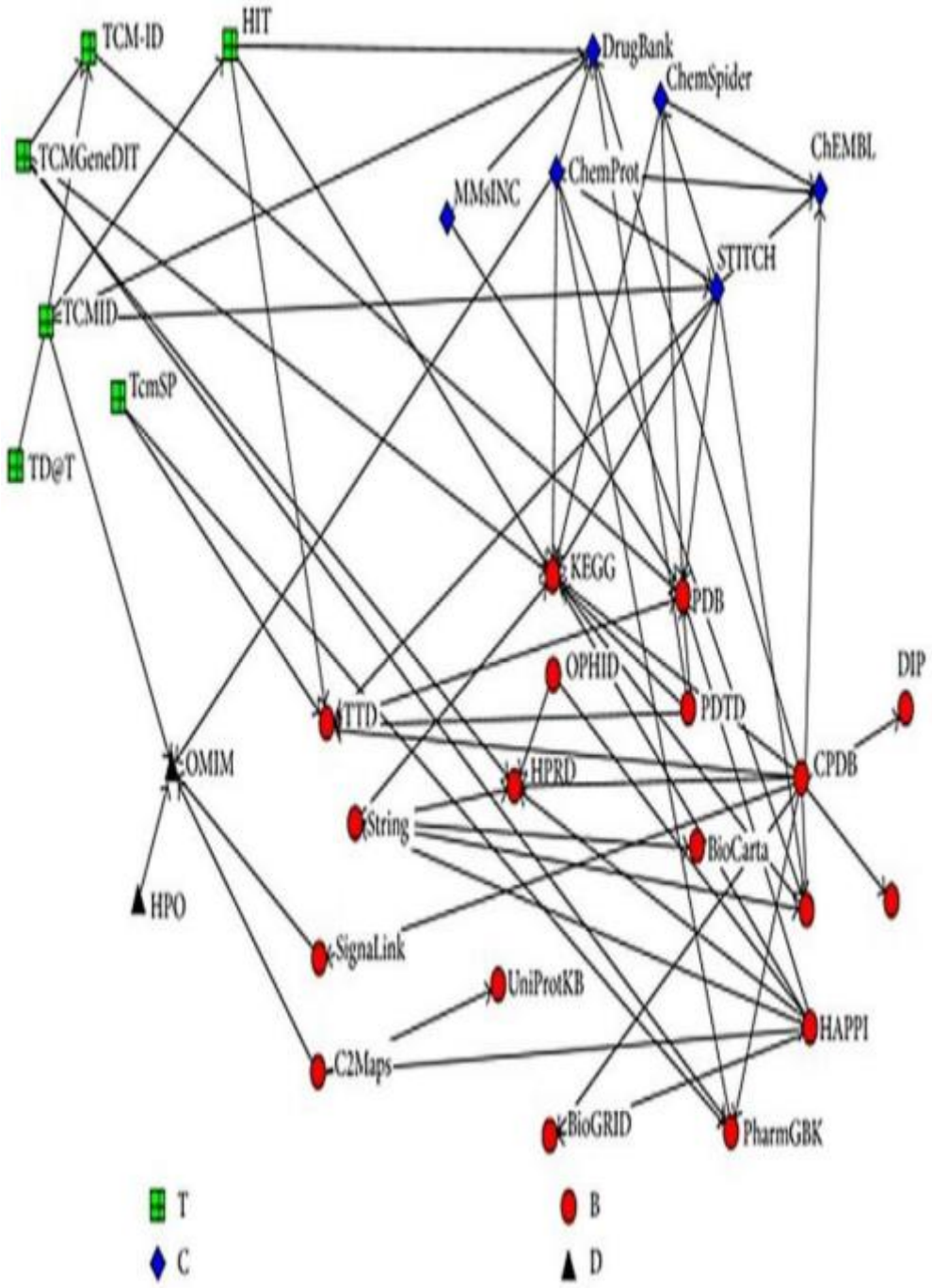


Fig : Database relationship network. Source Yang M , Chen, J-L,Xu,L-W.,2013. Navigatingtraditional Chinese medicine network pharmacology and computational tools .

Cytoscape , a Java-based open source software platform, is a useful tool for visualizing molecular interaction networks and integrating them with any type of attribute data. In addition to the basic set of features for data integration, analysis, and visualization, additional features are available in the form of apps, including network and molecular profiling analysis and links with other databases. In addition to Cytoscape, a number of visualization tools are available. Visual network pharmacology ,which is specially designed to visualize the complex relationships among diseases, targets, and drugs, mainly contains three functional modules: drug-centric, target-centric, and disease-centric VNP. This disease-target-drug database documents known connections among diseases, targets, and the USFDA-approved drugs. Users can search the database using disease, target, or drug name strings; chemical structures and substructures; or protein sequence similarity, and then obtain an online

interactive network view of the retrieved records. In the obtained network view, each node is a disease, target, or drug, and each edge is a known connection between two FIGURE 5.5 Database relationship network. [89] Navigating traditional Chinese medicine network pharmacology and computational tools. Evid. Based Complement Alternat. Med. 2013: 731969. Network Pharmacology Chapter | 5 145 of them. The Connectivity Map, or the CMap tool, allows the user to compare gene-expression profiles. The similarities or differences in the signature transcriptional expression profile and the small molecule transcriptional response profile may lead to the discovery of the mode of action of the small molecule. The response profile is also compared to response profiles of drugs in the CMap database with respect to the similarity of transcriptional responses. A network is constructed and the drugs that appear closest to the small molecule are selected to have better insight into the mode of action.

Other software, such as Gephi, an exploration platform for networks and complex systems, and Cell Illustrator, a Java-based tool specialized in biological processes and systems, can alsobe used for building networks .

Network Pharmacology: An Appropriate Approach for Modern TCM Research

Given the rapid progress in bioinformatics, systems biology, and polypharmacology, network-based drug discovery is considered to be a promising approach for cost-effective drug development. Systems biology examines biological systems by systematically perturbing them; monitoring the gene, protein, and informational pathway responses; integrating these data; and,

ultimately, formulating mathematical models to describe the structure of the system and its response to individual perturbations. Based on a systems biology approach, the concept of network pharmacology was first proposed. Because network pharmacology can provide a full or partial understanding of the principles of network theory and systems biology, it has been considered the next paradigm in drug discovery .Furthermore, the network pharmacology approach has been used to study “compound-proteins/genes-disease” pathways, which are capable of describing complexities among biological systems, drugs, and diseases from a network perspective, sharing a similar holistic philosophy as TCM. Applications of systems biology methods to determine the pharmacological action, mechanism of action, and safety of TCMs are invaluable for modern research and development of TCM. Thus, a new interdisciplinary method termed TCM network pharmacology has been proposed., which has initiated a new research paradigm for transforming TCM from an experience-based to evidence-based medicine. In this work, we first summarized the currently widely used databases and tools for TCM network pharmacology research. Second, we concentrated on the different applications of network pharmacology to TCM research, including TCM recipes, target prediction, and network toxicology.

3.7. NETWORK ETHNOPHARMACOLOGY OF TRIPHALA

Triphla is one of the most popular and widely used Ayurvedic formulations. Triphala contains fruits of three myrobalans: Emblica officinalis (EO; Amalaki) also known as Phyllanthus emblica; Terminalia bellerica (TB; Vibhitaka); and Terminalia chebula (TC; Haritaki). Triphala is the drug of choice for the treatment of several diseases, especially those of metabolism, dental, and skin conditions, and treatment of cancer. It has a very good effect on the health of heart, skin, eyes, and helps to delay degenerative changes, such as cataracts .Triphala can be used as an inexpensive and nontoxic natural product for the prevention and treatment of diseases where vascular endothelial growth factor Ainduced angiogenesis is involved .

The presence of numerous polyphenolic compounds empowers it with a broad antimicrobial spectrum[46]. Triphala is a constituent of about 1500 Ayurveda formulations and it can be used for several diseases. Triphala combats degenerative and metabolic disorders possibly through lipid peroxide inhibition and free radical scavenging[90]. In a phase I clinical trial on healthy volunteers, immunostimulatory effects of Triphala on cytotoxic T cells and natural killer cells

have been reported. Triphala is shown to induce apoptosis in tumor cells of the human pancreas,in both in vitro and in vivo models. Although the anticancer properties of Triphala have been studied, the exact mechanism of action is still not known. The beneficial role of Triphala in disease management of proliferative vitreoretinopathy has also been reported .One of the key ingredients of Triphala is Amalaki. Some studies have already shown the beneficial effect of Amalaki Rasayana to suppress neurodegeneration in fly models of Huntington's and Alzheimer's diseases . Triphala is an effective medicine to balance all three Dosha. It is considered as a good rejuvenator Rasayana, which facilitates nourishment to all tissues, or Dhatu. Here we demonstrate the multidimensional properties of Triphala using human proteome, diseasome, and microbial proteome targeting networks.

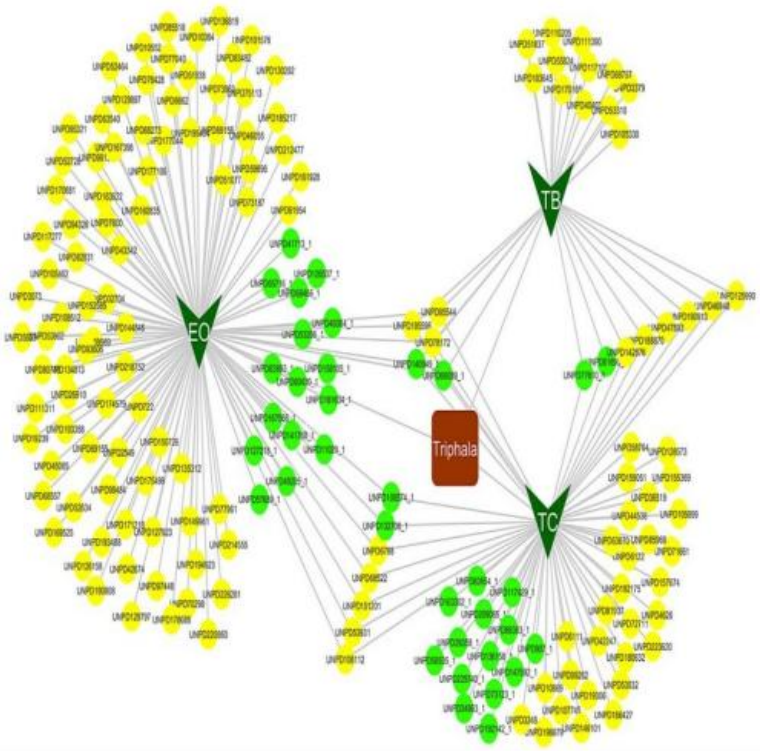
5.1 Triphala Bioactive

The botanicals of Triphala—EO, TB, and TC—contain 114, 25, and 63 bioactives, respectively, according to UNPD data collected during June 2015. Of these, a few bioactives are common among the three botanicals. Thus, Triphala formulation as a whole contains 177 bioactives. Out of these, 36 bioactives were Score-1, based on Binding DB search carried out during June 2015. EO, TB, and TC contain 20, 4, and 20 Score-1 bioactives, respectively . The Score-1 bioactives that are common among three plants are chebulanin, ellagic acid, gallussaeure, 1,6-digalloyl-beta-D-glucopiranoside, methyl gallate, and tannic acid. This bioactive information is the basic step toward constructing human proteome and microbial proteome targeting networks.[98]

5.2 Human Proteome and Diseasome Targeting Network of Triphala

Thirty-six Score-1 bioactives of Triphala are shown to interact with 60 human protein targets in 112 combinations (Fig. 5.1 , a,b). Quercetin, ellagic acid, 1,2,3,4,6-pentagalloylglucose and 1,2,3,6-tetrakis-(O-galloyl)-beta-D-glucose are the four bioactives that interact with the maximum number of targets: 21, 16, and 7, respectively. The other major bioactives that have multitargeting.[113] property include catechin; epicatechin; gallocatechin; kaempferol; and trans3,3',4',5,7-pentahydroxylflavane.

(A)



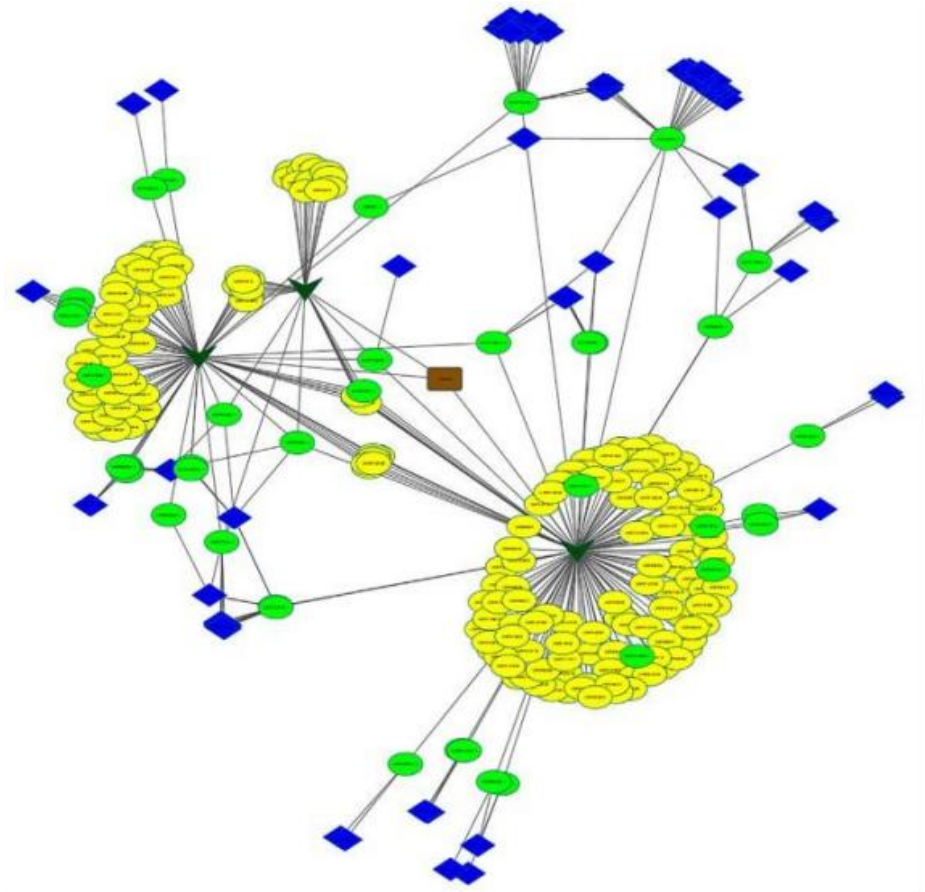


FIG 5.1 A and B Bioactive targets network of Triphala . Dark green versus are the botanicals of Triphala and oval nodes are the bioactives where green represent score 1 bioactives. Blue diamonds denote targets.

Include alkaline phosphatase (ALPL); carbonic anhydrase 7 (CA7); coagulation factor X (F10),DNA repair protein RAD51 homolog 1 (RAD51); GSTM1 protein (GSTM1); beta-secretase 1(BACE1); plasminogen activator inhibitor 1 (SERPINE1), prothrombin (F2); regulator of G- protein signaling (RGS) 4, 7, and 8, tissue-type plasminogen activator (PLAT); and tyrosine protein phosphatase nonreceptor type 2 (PTPN2). The 60 targets of Triphala are associated with 24 disease types, which include 130 disease indications

(b)

(Fig. 5.8). The major disease types in which Triphala targets are associated include cancers, cardiovascular diseases, nervous system diseases, and metabolic diseases. Analysis of existing data indicates that targets of

Triphala bioactives are involved in the 40 different types of cancers making it the largest groupof diseases, involving Triphala targets. This linkage is through the interaction of 25 bioactives and 27 target proteins in 46 different bioactivetarget combinations. The types of cancers which are networked by Triphala include pancreatic, prostate, breast, lung, colorectal and gastric cancers, tumors, and more. Quercetin, ellagic acid, pro delphinidin A1, and 1,2,3-benzenetriol are the important bioactives; and RAD51, BACE1, F2, MMP2, IGF1R, and EGFR are the important targets that play a role in cancer.

Triphala shows links to 18 indications of cardiovascular diseases through 12 bioactives and 11 targets. The cardiovascular diseases that are covered in the Triphala network include atherosclerosis, myocardial ischemia, infarction, cerebral vasospasm, thrombosis, and hypertension. The bioactives playing a major role in cardiovascular diseases are quercetin, 1,2,3,4,6-pentagalloyoglucose, 1,2,3,6-tetrakis-(O-galloyl)-beta-D-glucose, bellericagenin A1, and prodelphinidin A1, whereas the targets playing an important role are SERPINE1, F10, F2,

and FABP4. Triphala's network to nervous system disorders contains 13 diseases in which the significant ones are Alzheimer's disease, Parkinson's disease, diabetic neuropathy, and retinopathy. In this subnetwork, 14 bioactives interact with 11 targets through 21 different interactions. Quercetin, 1,2,3,4,6-pentagalloyoglucose, 1,2,3,6-tetrakis-(O-galloyl)-beta-D- glucose, and epigallocatechin-3-gallate are the most networked bioactives whereas the most networked targets are BACE1, SERPINE1, PLAT, ALDR, CA2. The association of Triphala with metabolic disorders is determined by six bioactives that interact with seven targets. The major metabolic diseases come in this link are obesity, diabetic complications, noninsulin- dependent diabetes, hypercholesterolemia, hyperlipidemia, and more. The bioactives having more interactions with targets are ellagic acid, quercetin, and bellericagenin A1, whereas the highly networked targets are IGF1R, FABP5, ALDR, and AKR1B1. Triphala bioactives are also linked to targets of other diseases comprising autoimmune diseases, ulcerative colitis, McCuneAlbright syndrome, psoriasis, gout, osteoarthritis, endometriosis, lung fibrosis, glomerulonephritis, and more. The proteome-targeting network of Triphala, thus, shows its ability to synergistically modulate 60 targets that are associated with 130 disease indications. This data is generated with the available information that included only one-fifth of the total number of bioactives. Further logical analysis and experimental studies based on the network result are needed to explore the in-depth mechanism of action of Triphala. For researchers in this area, these kind of networks can give an immense amount of information that can be developed further to reveal the real mystery behind the actions of traditional medicine.[101]

5.3 MICROBIAL PROTEOME TARGETING NETWORK OF TRIPHALA

Triphala is also referred to as a "tridoshic rasayana," as it balances the three constitutional elements of life. It tonifies the gastrointestinal tract, improves digestion, and is known to exhibit antiviral, antibacterial, antifungal, and antiallergic properties. Triphala Mashi was found to have nonspecific antimicrobial activity, as it showed a dose-dependent inhibition of Gram- positive and Gram-negative bacteria Hydroalcoholic, aqueous, and ether extracts of the three fruits of Triphala were reported to show antibacterial activity against uropathogens with a maximum drug efficacy recorded by the alcoholic extract The methanolic extract of Triphala showed the presence of 10 active compounds using GC-MS and also showed potent antibacterial and antifungal activity. Triphala has been well studied for its antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria, fungal species, and different strains of Salmonella typhi .Triphala showed significant antimicrobial activity against Enterococcus faecalis and Streptococcus mutans grown on tooth substrate thereby making it a suitable agent for prevention of dental plaque . The application of Triphala in commercial antimicrobial agents has been explored. A significant reduction in the colony forming units of oral streptococci was observed after 6% Triphala was incorporated in a mouthwash formulation . An ointment prepared from Triphala (10% (w/w)) showed significant antibacterial and wound healing activity in rats infected with Staphylococcus aureus, Pseudomonas aeruginosa, and Streptococcus pyogenes. The antiinfective network of Triphala sheds light on the efficacy of the formulation in the simultaneous targeting of multiple microorganisms. Also, this network provides information regarding some novel bioactivetarget combinations that can be explored to combat the problem of multidrug resistance. Among the bioactives of Triphala, 24 Score-1 bioactives target microbial proteins of 22 microorganisms. The botanicals of Triphala-EO, TB, and TCcontain 19, 3, and 8 Score1 bioactives respectively which showed interactions with microbial proteins. They act through modulation of 35 targets which are associated with diseases such as Leishmaniasis, malaria, tuberculosis, hepatitis C, acquired immunodeficiency syndrome (AIDS), cervical cancer, candidiasis, luminous vibriosis, yersiniosis, skin and respiratory infections, severe acute respiratory syndrome (SARS), avian viral infection, bacteremia, sleeping sickness, and anthrax. The microorganisms captured in the Triphala antiinfective network includes candida albicans, hepatitis C virus, human immunodeficiency virus 1, human papillomavirus type 16, human SARS coronavirus leishmania amazonensis, Mycobacterium tuberculosis, staphylococcus aureus, Plasmodium falciparum, and Yersinia

enterocolitica. In Mycobacterium tuberculosis, dTDP-4-dehydrorhamnose 3,5-epimerase RmlC is one of the four enzymes involved in the synthesis of dTDP-L-rhamnose, a precursor of L-rhamnose. The network shows that Triphala has the potential to modulate the protein through four bioactives such as punicalins, terflavin B, 4-O-(S)-flavogallonyl-6-O-galloylbeta-D-glucopyranose, and 4,6-O-(S,S)-gallagyl-alpha/beta-D-glucopyranose.[111]

3.8. Application of network pharmacology

NP has gained impetus as a novel paradigm for drug discovery. This approach using in silico data is fast becoming popular due to its cost efficiency and comparably good predictability. Thus, network analysis has various applications and promising future prospects with regard to the process of drug discovery and development. Table 5.2 lists the important applications of NP[114]

Applications of Network Pharmacology

Traditional medicine	• Scientific evidence for use of Ayurvedicmedicine • Understanding the rationale of traditionalformulations • Understanding the mechanism of action ofAyurvedic medicines • Safety and efficacy of Ayurvedicmedicines • Possible substitutes for endangeredbotanicals • Network-based designing and prescribingof plant formulations • Analysis of multiple bioactives, studyingsynergistic action • Botanical biomarkers for quality control
Pharmacology	• To develop new leads from natural products ● Understanding the mechanism of action of drugs • Determining the possible side effects of drugs ● Predicting new indications • Predicting toxicity • Predicting possible drugdrug interactions • Rational design of drugs based on group of interacting proteins • Drug repurposing
Drug research	• Identifying novel drug targets • Reduced cost and time through in silicoevaluation • Understanding the signaling pathway ofdisease types • Designing experiments based on drugs and targets • Therapeutics for multigene-dependentdiseases • Discovery of disease-causing genes • Diagnostic biomarkers • Studying drug resistance or antibioticresistance

3.9. LIMITATIONS AND SOLUTIONS

NP has proven to be a boon for drug research, and that helps in the revival of traditional knowledge. Albeit there are a few limitations of using NP for NP has proven to be a boon for drug research, and that helps in the revival of traditional knowledge. Albeit there are a few limitations of using NP for

1. NEP currently relies on various databases for literature and bioactive mining. Databases, though curated, may show discrepancies due to numerous sources of information, theoretical, and experimental data. Moreover, the botanicals that undergo certain preparatory procedures during the formulation of the medicine may have its constituents that have chemically changed due to the procedures; like boiling,

acid/ alkali reactions, interactions between the bioactives, etc. A way to navigate around this problem is to make use of modern, high-throughput chemical identification techniques like ultra-performance liquid chromatography electrospray ionizationt andem mass spectroscopy (UPLC-ESIMS/MS). This technique will help to identify the exact bioactives or the chemical constituents of the formulation, and will enrich the subsequent NEP studies. This is because the bioactives form the foundation of any traditional medicine network.

2. Absorption, distribution, metabolism, excretion, and toxic effects (ADMET) parameters associated with the bioactives/formulation when they are administered in the form of the medicine need to be considered in order to extrapolate in silico and cheminformatics data to in vitro and in vivo models. In silico tools that offer the prediction of these parameters can be depended on for this. But traditional medicines are generally accompanied by a vehicle for delivery of the medicine. These vehicles, normally various solvents—water, milk, lemon juice, butter, ghee (clarified butter), honey—that alter the solubility of the bioactives, play a role in regulating ADMET parameters. Experimental validation studies are required to evaluate this principle of traditional medicine.
3. Target identification usually relies on a single or a few databases due to the limited availability of databases with free access. This can occasionally give incomplete results. Also, there may be novel targets waiting to be discovered that could be a part of the mechanism of action of the bioactives. To deal with this discrepancy in the network, multiple databases should be considered for target identification. Integration of databases serving similar functions can also be a solution for this problem. In addition to this, experimental validation of the target molecules using protein protein interaction studies or gene expression studies will provide concrete testimony to the network predictions.
4. A number of traditional medicines act through multiple bioactives and targets. Synergy in botanical drugs helps to balance out the extreme pharmacological effects that individual bioactives may have. The interactions of bioactives with various target proteins, their absorption into the body after possible enzyme degradation, their transport, and finally their physiological effect are a crucial part of traditional medicine. However, in vitro assays or in silico tools are unable to give a clear idea as to the complete and exact interactions in a living organism. NP is only the cardinal step toward understanding the mechanism of bioactives /formulations. But this gives an overview of the action of traditional medicine which can be used to design in vivo experiments and clinical trials. This saves time and cost of research and inventions.
5. It is observed that formulations are working by simultaneous modulation of multiple targets. This modulation includes activation of some targets and inhibition of other. In order to understand this complex synergistic activity of formulation, investigative studies regarding the interactions of ligands with targets are to be carried out. This can be achieved by implementing high-throughput omics studies based on the network data.[100]

3.10 CONCLUSION

Network pharmacological analysis presents an immense scope for exploring traditional knowledge to find solutions for the current problems challenging the drug discovery industry. NEP can also play a key role in new drug discovery, drug repurposing, and rational formulation discovery. Many of the bioactivetarget combinations have been experimentally studied. The data synthesis using NP provides information regarding the mode of action of traditional medicine formulations, based on their constituent bioactives. This is a kind of reverse approach to deduce the molecular mechanism of action of formulations using modern, integrated technologies. The current network analysis is based on the studies that have been conducted and the literature that is available. Hence, the data is inconclusive as a number of studies are still underway and novel data is being generated continuously. Despite its limitations, this still is a favorable approach, as it gives insight into the hidden knowledge of our ancient traditional medicine wisdom. NP aids the logical analysis of this wisdom that can be utilized to understand the knowledge as well as to invent novel solutions for current pharmacological problems.

' REFERENCE

Wang J, et al. Sheng Li Ke Xue Jin Zhan. 2011. https://pubmed.ncbi.nlm.nih.gov/21351485/ .

Uma Uma Chandran, Neelay Mehendale, Saniya Patil, Rathnam Chaguturu and Bhushan Patwardhan Savitribai Phule Pune University, Pune, Maharashtra, India .

3. https://doi.org/10.1016/B978-0-12-801814-9.00005-2

Cheng, B.F., Hou, Y.Y., Jiang, M., Zhao, Z.Y., Dong, L.Y., Bai, G., 2013. Anti- inflammatory mechanism of qingfei xiaoyan wan studied with network pharmacology. Yao Xue Xue Bao 48, 686693.

Clark, D.E., Grootenhuis, P.D.J., 2002. Progress in computational methods for the prediction of ADMET properties. Curr. Opin. Drug Discov. Devel. 5, 382390.

Clark, D.E., Pickett, S.D., 2000. Computational methods for the prediction of "drug- likeness.". Drug Discov. Today 5, 4958.

Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., et al., 2011. Reactome: a database of reactions, pathways and biological processes. Nucl. Acids Res. 39.

http://www.drugbank.ca

http://bidd.nus.edu.sg/group/ttd/ttd.asp

http://matador.embl.de

https://www.ebi.ac.uk/chembldb

http://stitch.embl.de

http://bioinf-apache.charite.de/supertarget_v2

http://tdrtargets.org

http://www.dddc.ac.cn/pdtd

http://integrity.thomson-pharma.com

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/Adverse Drug Effects/default.htm

http://sideeffects.embl.de

http://www.japic.or.jp

http://chembank.broadinstitute.org

http://crdd.osdd.net/raghava/cancerdr

http://www.bindingdb.org/bind

http://zinc.docking.org

https://cansar.icr.ac.uk

http://asdcd.amss.ac.cn

http://www.genome.jp/tools/dinies

http://prediction.charite.de

http://www.swisstargetprediction.ch

Russom, P., Big data analytics. TDWI best practices report, fourth quarter, 2011, 19, 40.

Zhang, W., Pattern classification and recognition of invertebrate functional groups using self-organizing neural networks. Environmental monitoring and assessment, 2007, 130, (1),415-422.

GAASTERLAND, T.; RAGAN, M.A., Microbial genescapes: phyletic and functional patterns of ORF distribution among prokaryotes. Microbial & comparative genomics, 1998, 3, (4), 199- 217.

Dandekar, T.; Snel, B.; Huynen, M.; Bork, P., Conservation of gene order: a fingerprint of proteins that physically interact. Trends in biochemical sciences, 1998, 23, (9), 324-328.

Marcotte, E.M.; Pellegrini, M.; Ng, H.-L.; Rice, D.W.; Yeates, T.O.; Eisenberg, D., Detecting protein function and protein-protein interactions from genome sequences. Science (New York, N.Y.), 1999, 285, (5428), 751-753.

Fryxell, K.J., The coevolution of gene family trees. Trends in Genetics, 1996, 12, (9), 364-369

Göbel, U.; Sander, C.; Schneider, R.; Valencia, A., Correlated mutations and residue contacts in proteins. Proteins: Structure, Function, and Bioinformatics, 1994, 18, (4), 309-317.

Aloy, P.; Russell, R.B., InterPreTS: protein interaction prediction through tertiary structure.Bioinformatics (Oxford, England), 2003, 19, (1), 161-162.

Bock, J.R.; Gough, D.A., Predicting protein–protein interactions from primary structure. Bioinformatics (Oxford, England), 2001, 17, (5), 455-460.

Zhang, W., Network Biology: an exciting frontier science. Network Biology, 2011, 1, (1),79-80.

Dobson, C.M., Chemical space and biology. Nature, 2004, 432, (7019), 824-828.

Kanehisa, M.; Goto, S.; Hattori, M.; Aoki-Kinoshita, K.F.; Itoh, M.; Kawashima, S.; Katayama, T.; Araki, M.; Hirakawa, M., From genomics to chemical genomics: new developments in KEGG. Nucleic acids research, 2006, 34, (suppl 1), D354-D357.

Stockwell, B.R., Chemical genetics: ligand-based discovery of gene function. Nature Reviews Genetics, 2000, 1, (2), 116-125.

Wheeler, D.L.; Barrett, T.; Benson, D.A.; Bryant, S.H.; Canese, K.; Chetvernin, V.; Church, D.M.; DiCuccio, M.; Edgar, R.; Federhen, S., Database resources of the national center for biotechnology information. Nucleic acids research, 2007, 35, (suppl 1), D5-D12.

Haggarty, S.J.; Koeller, K.M.; Wong, J.C.; Butcher, R.A.; Schreiber, S.L., Multidimensional chemical genetic analysis of diversityoriented synthesis-deriveddeacetylase inhibitors using cell-based assays. Chemistry & biology, 2003, 10, (5), 383- 396.

Kuruvilla, F.G.; Shamji, A.F.; Sternson, S.M.; Hergenrother, P.J.; Schreiber, S.L., Dissecting glucose signalling with diversityoriented synthesis and small-molecule microarrays. Nature, 2002, 416, (6881), 653-657.

Yamanishi, Y.; Araki, M.; Gutteridge, A.; Honda, W.; Kanehisa, M., Prediction of drug– target interaction networks from the integration of chemical and genomic spaces. Bioinformatics (Oxford, England), 2008, 24, (13), i232-i240.

Schomburg, I.; Chang, A.; Ebeling, C.; Gremse, M.; Heldt, C.; Huhn, G.; Schomburg, D., BRENDA, the enzyme database: updates and major new developments. Nucleic acids research, 2004, 32, (suppl 1), D431-D433.

Wishart, D.S.; Knox, C.; Guo, A.C.; Cheng, D.; Shrivastava, S.; Tzur, D.; Gautam, B.; Hassanali, M., DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic acids research, 2007, 36, (suppl_1), D901-D906 .

Hattori, M.; Okuno, Y.; Goto, S.; Kanehisa, M., Development of a chemical structure comparison method for integrated analysis of chemical and genomic information in the metabolic pathways. Journal of the American Chemical Society, 2003, 125, (39), 11853- 11865.

Cheng, A.C.; Coleman, R.G.; Smyth, K.T.; Cao, Q.; Soulard, P.; Caffrey, D.R.; Salzberg, A.C.; Huang, E.S., Structure-based maximal affinity model predicts small-molecule drug ability. Nature biotechnology, 2007, 25, (1), 71-75.

Rarey, M.; Kramer, B.; Lengauer, T.; Klebe, G., A fast flexible docking method using an incremental construction algorithm. Journal of molecular biology, 1996, 261, (3), 470-489.

Liebler, D.C.; Guengerich, F.P., Elucidating mechanisms of druginduced toxicity. Nature reviews Drug discovery, 2005, 4, (5), 410- 420.

Blagg, J., Structure–activity relationships for in vitro and in vivo toxicity. Annual Reportsin Medicinal Chemistry, 2006, 41, 353- 368.

Whitebread, S.; Hamon, J.; Bojanic, D.; Urban, L., Keynote review: in vitro safety pharmacology profiling: an essential tool for successful drug development. Drug discoverytoday, 2005, 10, (21), 1421-1433.

Ashburn, T.T.; Thor, K.B., Drug repositioning: identifying and developing new uses for existing drugs. Nature reviews Drug discovery, 2004, 3, (8), 673-683.

Campillos, M.; Kuhn, M.; Gavin, A.-C.; Jensen, L.J.; Bork, P., Drug target identification using side-effect similarity. Science (New York, N.Y.), 2008, 321, (5886), 263-266.

Finlayson, K.; Witchel, H.J.; McCulloch, J.; Sharkey, J., Acquired QT interval prolongation and HERG: implications for drug discovery and development. European journal of pharmacology, 2004, 500, (1), 129-142.

Tatonetti, N.P.; Liu, T.; Altman, R.B., Predicting drug side-effects by chemical systems biology. Genome biology, 2009, 10, (9), 238.

Cheng, F.; Li, W.; Wang, X.; Zhou, Y.; Wu, Z.; Shen, J.; Tang, Y., Adverse drug events: database construction and in silico prediction. Journal of chemical information and modeling, 2013, 53, (4), 744- 752.

Cheng, F.; Li, W.; Wu, Z.; Wang, X.; Zhang, C.; Li, J.; Liu, G.; Tang, Y., Prediction of polypharmacological profiles of drugs by the integration of chemical, side effect, and therapeutic space. Journal of chemical information and modeling, 2013, 53, (4), 753- 762.

Yamanishi, Y.; Kotera, M.; Kanehisa, M.; Goto, S., Drug-target interaction prediction fromchemical, genomic and pharmacological data in an integrated framework. Bioinformatics (Oxford, England), 2010, 26, (12), i246-i254.

Scheiber, J.; Jenkins, J.L.; Sukuru, S.C.K.; Bender, A.; Mikhailov, D.; Milik, M.; Azzaoui,K.; Whitebread, S.; Hamon, J.; Urban, L., Mapping adverse drug reactions in chemical space. Journal of medicinal chemistry, 2009, 52, (9), 3103-3107.

Yamanishi, Y. In Advances in Neural Information Processing Systems, 2009, pp 1841- 1848.

Tobinick, E.L., The value of drug repositioning in the current pharmaceutical market. Drugnews & perspectives, 2009, 22, (2), 119-125.

Bandekar, M.; Anwikar, S.; Kshirsagar, N., Quality check of spontaneous adverse drug reaction reporting forms of different countries. Pharmacoepidemiology and drug safety, 2010, 19, (11), 1181-1185.

Yang, L.; Xu, L.; He, L., A CitationRank algorithm inheriting Google technology designed to highlight genes responsible for serious adverse drug reaction. Bioinformatics (Oxford, England), 2009, 25, (17), 2244-2250.

Rognan, D., Structure!based approaches to target fishing and ligand profiling. Molecular informatics, 2010, 29, (3), 176-187.

Berger, S.I.; Iyengar, R., Role of systems pharmacology in understanding drug adverse events. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2011, 3, (2), 129-135.

De Franchi, E.; Schalon, C.; Messa, M.; Onofri, F.; Benfenati, F.; Rognan, D., Binding of protein kinase inhibitors to synapsin I inferred from pair-wise binding site similarity measurements. PloS one, 2010, 5, (8), e12214.

Keiser, M.J.; Setola, V.; Irwin, J.J.; Laggner, C.; Abbas, A.I.; Hufeisen, S.J.; Jensen, N.H.; Kuijer, M.B.; Matos, R.C.; Tran, T.B., Predicting new molecular targets for known drugs. Nature, 2009, 462, (7270), 175-181. [88] Li, Y.Y.; An, J.; Jones, S.J., A large-scale computational approach to drug repositioning. Genome Informatics, 2006, 17, (2), 239- 247.

Lee, S.; Park, K.; Kim, D., Building a drug–target network and its applications. Expert opinion on drug discovery, 2009, 4, (11), 1177-1189.

Ma, X.H.; Shi, Z.; Tan, C.; Jiang, Y.; Go, M.L.; Low, B.C.; Chen, Y.Z., In-Silico approaches to multi-target drug discovery. Pharmaceutical research, 2010, 27, (5), 739- 749.

Keiser, M.J.; Irwin, J.J.; Shoichet, B.K., The chemical basis of pharmacology. Biochemistry, 2010, 49, (48), 10267-10276.

Yang, L.; Chen, J.; He, L., Harvesting candidate genes responsible for serious adverse drug reactions from a chemical-protein interactome. PLoS computational biology, 2009, 5, (7),e1000441.

Rich, R.L.; Day, Y.S.; Morton, T.A.; Myszka, D.G., Highresolution and high-throughput protocols for measuring drug/human serum albumin interactions using BIACORE. Analytical biochemistry, 2001, 296, (2), 197-207.

Von Rechenberg, M.; Blake, B.K.; Ho, Y.S.J.; Zhen, Y.; Chepanoske, C.L.; Richardson, B.E.; Xu, N.; Kery, V., Ampicillin/penicillin!binding protein interactions as a model drug!target system to optimize affinity pull!down and mass spectrometric strategies for target and pathway identification. Proteomics, 2005, 5, (7), 1764-1773.

Ji, Z.L.; Han, L.Y.; Yap, C.W.; Sun, L.Z.; Chen, X.; Chen, Y.Z., Drug Adverse Reaction Target Database (DART). Drug safety, 2003, 26, (10), 685-690.

Zhang, J.-X.; Huang, W.-J.; Zeng, J.-H.; Huang, W.-H.; Wang, Y.; Zhao, R.; Han, B.-C.; Liu, Q.-F.; Chen, Y.-Z.; Ji, Z.-L., DITOP: drug-induced toxicity related protein database. Bioinformatics (Oxford, England), 2007, 23, (13), 1710-1712.

Chen, X.; Ji, Z.L.; Chen, Y.Z., TTD: therapeutic target database. Nucleic acids research, 2002, 30, (1), 412-415.

Chen, X.; Ji, Z.L.; Chen, Y.Z., TTD: therapeutic target database. Nucleic acids research, 2002, 30, (1), 412-415.

Mallal, S.; Phillips, E.; Carosi, G.; Molina, J.-M.; Workman, C.; Tomažič, J.; Jägel-Guedes, E.; Rugina, S.; Kozyrev, O.; Cid, J.F., HLA-B* 5701 screening for hypersensitivity to abacavir. New England Journal of Medicine, 2008, 358, (6), 568-579.

Martin, A.M.; Nolan, D.; Gaudieri, S.; Almeida, C.A.; Nolan, R.; James, I.; Carvalho, F.; Phillips, E.; Christiansen, F.T.; Purcell, A.W., Predisposition to abacavir hypersensitivity conferred by HLA-B* 5701 and a haplotypic Hsp70-Hom variant. Proceedings of the National Academy of Sciences, 2004, 101, (12), 4180-4185.

Chessman, D.; Kostenko, L.; Lethborg, T.; Purcell, A.W.; Williamson, N.A.; Chen, Z.; Kjer-Nielsen, L.; Mifsud, N.A.; Tait, B.D.; Holdsworth, R., Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of a systemic drug hypersensitivity. Immunity, 2008, 28, (6), 822-832.

Stewart-Jones, G.B.; Gillespie, G.; Overton, I.M.; Kaul, R.; Roche, P.; McMichael, A.J.; Rowland-Jones, S.; Jones, E.Y., Structures of three HIV-1 HLA-B* 5703-peptide complexes and identification of related HLAs potentially associated with long-term nonprogression. The Journal of Immunology, 2005, 175, (4), 2459-2468.

Luo, H.; Chen, J.; Shi, L.; Mikailov, M.; Zhu, H.; Wang, K.; He, L.; Yang, L., DRAR-CPI: a server for identifying drug repositioning potential and adverse drug reactions via the chemical–protein interactome. Nucleic acids research, 2011, 39, (suppl 2), W492- W498.

Lamb, J.; Crawford, E.D.; Peck, D.; Modell, J.W.; Blat, I.C.; Wrobel, M.J.; Lerner, J.; Brunet, J.-P.; Subramanian, A.; Ross, K.N., The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science (New York, N.Y.), 2006, 313, (5795), 1929-1935.

Yang, L.; Luo, H.; Chen, J.; Xing, Q.; He, L., SePreSA: a server for the prediction of populations susceptible to serious adverse drug reactions implementing the methodology of a chemical–protein interactome. Nucleic acids research, 2009, 37, (suppl 2), W406- W412.

Young, P.W.; Buckle, D.R.; Cantello, B.C.; Chapman, H.; Clapham, J.C.; Coyle, P.J.; Haigh, D.; Hindley, R.M.; Holder, J.C.; Kallender, H., Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor γ.Journal of Pharmacology and Experimental Therapeutics, 1998, 284, (2), 751-759.

Chen, H.; Wang, X.; Jin, H.; Liu, R.; Hou, T., Discovery of the molecular mechanisms of the novel chalcone-based Magnaporthe oryzae inhibitor C1 using transcriptomic profilingand coexpression network analysis. SpringerPlus, 2016, 5, (1), 1851.

Shu, M.; Zai, X.; Zhang, B.; Wang, R.; Lin, Z., Hypothyroidism side effect in patients treated with sunitinib or sorafenib: clinical and structural analyses. PloS one, 2016, 11, (1),e0147048.

Ye, X.-y.; Ling, Q.-z.; Chen, S.-j., Identification of a potential target of capsaicin by computational target fishing. Evidence-Based Complementary and Alternative Medicine, 2015, 2015.

Iyer, P.; Bolla, J.; Kumar, V.; Gill, M.S.; Sobhia, M.E., In silico identification of targets for a novel scaffold, 2-thiazolylimino-5- benzylidin-thiazolidin-4-one. Molecular diversity,2015, 19, (4), 855-870.

Qiu, J.-X.; Zhou, Z.-W.; He, Z.-X.; Zhao, R.J.; Zhang, X.; Yang, L.; Zhou, S.-F.; Mao, Z.- F., Plumbagin elicits differential proteomic responses mainly involving cell cycle, apoptosis, autophagy, and epithelial-to-mesenchymal transition pathways in human prostate cancer PC-3 and DU145 cells. Drug design, development and therapy, 2015, 9, 349.

Su, J.; Chang, C.; Xiang, Q.; Zhou, Z.-W.; Luo, R.; Yang, L.; He, Z.-X.; Yang, H.; Li, J.; Bei, Y., Xyloketal B, a marine compound, acts on a network of molecular proteins and regulates the activity and expression of rat cytochrome P450 3a: a bioinformatic and animal study. Drug design, development and therapy, 2014, 8, 2555.

Chen, S.-J., A potential target of Tanshinone IIA for acute promyelocytic leukemia revealed by inverse docking and drug repurposing. Asian Pacific journal of cancer prevention : APJCP, 2014, 15, (10), 4301-4305.

Qi, L.; Ding, Y., Potential antitumor mechanisms of phenothiazine drugs. Science China Life Sciences, 2013, 56, (11), 1020-1027.

Faraone, S.V.; Zhang!James, Y., Can sodium/hydrogen exchange inhibitors be repositioned for treating attention deficit hyperactivity disorder? An in silico approach. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2013, 162, (7), 711-717.

Zhou, T.; Su, R.-Q.; Liu, R.-R.; Jiang, L.-L.; Wang, B.-H.; Zhang, Y.-C., Accurate and diverse recommendations via eliminating redundant correlations. New Journal of Physics,2009, 11, (12), 123008.

Zhou, T.; Kuscsik, Z.; Liu, J.-G.; Medo, M.; Wakeling, J.R.; Zhang, Y.-C., Solving the apparent diversity-accuracy dilemma of recommender systems. Proceedings of the National Academy of Sciences, 2010, 107, (10), 4511-4515.

Sarwar, B.; Karypis, G.; Konstan, J.; Riedl, J. In Proceedings of the 10th international conference on World Wide Web; ACM, 2001, pp 285-295.

Herlocker, J.L.; Konstan, J.A.; Terveen, L.G.; Riedl, J.T., Evaluating collaborative filtering recommender systems. ACM Transactions on Information Systems (TOIS), 2004,22, (1), 5-53

Cheng, F.; Liu, C.; Jiang, J.; Lu, W.; Li, W.; Liu, G.; Zhou, W.; Huang, J.; Tang, Y., Prediction of drug-target interactions and drug repositioning via network-based inference.PLoS computational biology, 2012, 8, (5), e1002503.

Cheng, F.; Zhou, Y.; Li, W.; Liu, G.; Tang, Y., Prediction of chemical-protein interactions network with weighted networkbased inference method. PloS one, 2012, 7, (7),e41064.

Jia, C.-X.; Liu, R.-R.; Sun, D.; Wang, B.-H., A new weighting method in network- based recommendation. Physica A: Statistical Mechanics and its Applications, 2008, 387,(23), 5887-5891.

Wu, Z.; Cheng, F.; Li, J.; Li, W.; Liu, G.; Tang, Y., SDTNBI: an integrated network and chemoinformatics tool for systematic prediction of drug–target interactions and drug repositioning. Briefings in bioinformatics, 2016, bbw012.

Cheng, F.; Zhou, Y.; Li, J.; Li, W.; Liu, G.; Tang, Y., Prediction of chemical–protein interactions: multitarget-QSAR versus computational chemogenomic methods. MolecularbioSystems, 2012, 8, (9), 2373-2384.

Shen, J.; Cheng, F.; Xu, Y.; Li, W.; Tang, Y., Estimation of ADME properties with substructure pattern recognition. Journal of chemical information and modeling, 2010, 50,(6), 1034-1041.

Yamanishi, Y.; Pauwels, E.; Saigo, H.; Stoven, V., Extracting sets of chemical substructures and protein domains governing drugtarget interactions. Journal of chemical information and modeling, 2011, 51, (5), 1183-1194.

Klekota, J.; Roth, F.P., Chemical substructures that enrich for biological activity. Bioinformatics (Oxford, England), 2008, 24, (21), 2518-2525.

Wu, Z.; Lu, W.; Wu, D.; Luo, A.; Bian, H.; Li, J.; Li, W.; Liu, G.; Huang, J.; Cheng, F., In silico prediction of chemical mechanism of action via an improved network! based inference method. British journal of pharmacology, 2016, 173, (23), 3372-3385.

Jahchan, N.S.; Dudley, J.T.; Mazur, P.K.; Flores, N.; Yang, D.; Palmerton, A.; Zmoos, A.-F.; Vaka, D.; Tran, K.Q.; Zhou, M., A drug repositioning approach identifies tricyclic antidepressants as inhibitors of small cell lung cancer and other neuroendocrine tumors. Cancer discovery, 2013, 3, (12), 1364-1377.

Shchors, K.; Massaras, A.; Hanahan, D., Dual targeting of the autophagic regulatory circuitry in gliomas with repurposed drugs elicits cell-lethal autophagy and therapeutic benefit. Cancer cell, 2015, 28, (4), 456-471.

Cheng, F.; Hong, H.; Yang, S.; Wei, Y., Individualized networkbased drug repositioning infrastructure for precision oncology in the panomics era. Briefings in bioinformatics, 2016, bbw051.

Li, J.; Lei, K.; Wu, Z.; Li, W.; Liu, G.; Liu, J.; Cheng, F.; Tang, Y., Network-based identification of microRNAs as potential pharmacogenomic biomarkers for anticancer drugs. Oncotarget, 2016, 7, (29), 45584.

Chen, X.; Liu, M.X.; Yan, G.Y., Drug-target interaction prediction by random walk onthe heterogeneous network. Molecular bio Systems, 2012, 8, (7), 1970-1978.

Wang, L.; You, Z.H.; Chen, X.; Yan, X.; Liu, G.; Zhang, W., RFDT: A Rotation Forest-based Predictor for Predicting DrugTarget Interactions using Drug Structure and Protein Sequence Information. Current protein & peptide science, 2016.

Huang, Y.A.; You, Z.H.; Chen, X., A systematic prediction of drug-target interactions using molecular fingerprints and protein sequences. Current protein & peptide science, 2016.