Published Online on 4 June 2015

Proc Indian Natn Sci Acad **81** No. 3 June 2015 pp. 561-568
© *Printed in India*.
DOI: 10.16943/ptinsa/2015/v81i3/48229

Emerging Techniques

Network Pharmacology: An Emerging Technique for Natural Product Drug Discovery and Scientific Research on Ayurveda

UMA CHANDRAN[1], NEELAY MEHENDALE[2], GIRISH TILLU[1] and BHUSHAN PATWARDHAN[1*]
[1]Interdisciplinary School of Health Sciences, [2]Institute of Bioinformatics and Biotechnology, Savitribai Phule Pune University, Ganeshkhind, Pune 411 007, India

(Received on 03 May 2015; Revised on 18 May 2015; Accepted on 20 May 2015)

Natural products from traditional medicine like Ayurveda are considered as attractive options in new drug discovery. Traditional poly herbal formulations contain many bioactives and are capable of modulating several disease targets. Studying complex relationships between the bioactives, targets, diseases and genes is now possible with help of emerging technique known as network pharmacology. This article briefly explains present status of drug research and highlights importance of network pharmacology as a new tool for drug and formulation discovery. Already, network pharmacology has been successfully used to study traditional Chinese medicines. With help of Ayurvedic formulation Triphala, this article demonstrates how pharmacology networks of medicinal plants and their formulations can be constructed and used to understand putative actions, indications and mechanisms. The emerging technique of network pharmacology can serve as a valuable tool for scientific understanding of Ayurveda and natural product drug discovery.

Key Words: Ayurveda; Bioactives; Botanicals, Drug Discovery; Herbal Formulations; Poly Pharmacology; Targets; Traditional Medicine; Triphala

Introduction

Natural Product Discovery

Drug research has undergone several transitions during the last few years. Although high throughput technologies are available, the number of new chemical entities entering in market as drugs has been reduced. Moreover, the number of drugs being withdrawn after launching in the markets is increasing. There seems to be a need to rediscover discovery process (Patwardhan, 2014). Traditional knowledge and natural products can play an important role to overcome present impasse in drug discovery (Patwardhan and Mashelkar, 2009). It is estimated that over one hundred new, natural product-based leads are in clinical development (Harvey, 2008). About 60% of anticancer and 75% of anti-infective drugs approved from 1981 to 2002 have natural origins (Gupta *et al.*, 2005). Many active compounds (bioactives) from traditional medicine sources could serve as good starting compounds and scaffolds for rational drug design. Most of these compounds are part of routinely-used, traditional medicines and hence their tolerance and safety are relatively better known than any other chemical entities that are new for human use.

Many experts feel that it would be cheaper and more efficient to study plants described in ancient texts (Holland, 1994). In the past, impressive successes with bioactives from botanicals (medicinal plants) have been reported. Most notably among

**Author for Correspondence: E-mail: bpatwardhan@gmail.com*

these include quinghaosu and artemisinin from Chinese medicine. Numerous bioactive molecules have come out of the Ayurvedic medicines including Rauwolfia alkaloids for treating hypertension, psoralens for vitiligo, Holarrhena alkaloids for amebiasis, guggulsterons as hypolipidemic agents, *mucuna pruriens* for Parkinson's disease, piperidines as bioavailability enhancers, baccosides in mental retention, picrosides for hepatic protection, phyllanthins as antivirals, curcumine for inflammation and withanolides as immunomodulators (Patwardhan *et al*., 2004).

New Trends in Drug Discovery

Normally drug discovery follows the one gene/one target/one drug approach, however, a multi-target, multi-ingredient formulation design may be the smarter approach. Drug discovery need not be confined always to the discovery of a single molecule. Today, we are dealing with polygenic syndromes and not just isolated diseases, hence multi-target approaches are necessary (Zimmermann *et al*., 2007). Lifestyle disorders like obesity, diabetes, cardiovascular diseases and cancers can be managed with multi-targeted approach. Due to the diversity of structures, botanical extracts can deal with multiple targets simultaneously and may have synergistic effects. Therefore, the development of standardized, synergistic, safe and effective herbal formulations with sufficient scientific evidence can offer an economical and better alternative.

Advances in omics technologies, computational and systems biology have provided new insights in identifying multiple target modulations (Gu *et al*., 2013a). For example, curcumin is reported to regulate multiple targets and cell signaling pathways such as cyclooxygenase-2, tumor necrosis factor (TNF-α), epidermal growth factor, human epidermal growth factor receptor 2, vascular endothelial cell growth factor and proteasome; and activate apoptosis, down-regulate cell survival gene products, up-regulate tumor suppressor protein-p53 and cyclin-dependent kinase inhibitors showing its potential in the disease conditions like cancer, diabetes and Alzheimer's disease (Gupta *et al*., 2013).

Panax ginseng has been reported to modulate multiple targets in type 2 diabetes mellitus (T2DM) and insulin resistance such as insulin receptor substrate-1, c-Jun NH2-terminal kinase, 5' adenosine monophosphate-activated protein kinase, phosphatidylinositol 3-kinase (PI3K), Akt/PKB, Thr308, Ser473 and glucose transporter type 4 (GLUT 4). Through these targets it is modulating the uptake and disposal of glucose in adipocytes (Zhang *et al*., 2008).

We propose that formulations from traditional systems like Ayurveda might be useful in polygenic lifestyle and chronic disorders. A change in the discovery strategy from a single target, new chemical entity as a drug to multiple-target, synergistic formulation discovery has been proposed (Patwardhan *et al*., 2015).

Emerging Technique

Network Pharmacology

Recently, a new technique known as poly-pharmacology has emerged which is able to address the limitations with current drug discovery challenges. Poly-pharmacology, also known as network pharmacology, attempts to understand drug action and interactions with multiple targets (Hopkins, 2007). It uses computational power and computer-based virtual high-throughput screening for docking studies to improve the efficiency of discovery process. Network pharmacology also attempts repurposing existing drug molecules for different therapeutic conditions. However, these efforts require some guidance for selecting the right type of targets and new scaffolds of drug molecules. Integrating systems biology and network pharmacology can accelerate search for drug targets and help in designing new drugs, which can modulate multiple biological targets (Hopkins, 2008; Cho *et al*., 2012). A concept of 'network target' has been proposed to help design and predict the best possible treatments (Li, 2007; Li *et al*., 2011). The constructed network system can predict the main active components, and their corresponding targets, which can be helpful for the therapeutic applications of complex formulations of traditional medicine (Shi *et al*., 2014).

The traditional knowledge can play the vital role in this process of formulation discovery and the repurposing of existing drugs (Ellingson *et al*., 2014). Multi ingredient traditional formulations with several bioactives have putative synergistic activities probably through interaction with multiple target proteins, diverse genes and regulation of multiple signaling pathways. Generally, understanding such complex pharmacological mechanisms is difficult. Network pharmacology technique has been used to understand mechanisms of Traditional Chinese Medicines (TCM) (Yang *et al*., 2012). Synergistic activity of TCM formulations like Qing-Luo-Yin and Liu-Wei-Di-Huang pill have been studied using network pharmacology (Li and Zhang, 2013). Recently, the molecular mechanisms of TCM herbal formula known as Guizhi-Shaoyao-Zhimu used in the treatment of diabetic peripheral neuropathy has been studied with network pharmacology (Zhao *et al*., 2015).

Many Chinese researchers are now exploring pharmacological mechanisms of complex botanical formulations from TCM (Hao and Xiao, 2014; Li *et al*., 2012). Cardiovascular disease herb database (CVDHD) which integrates medicinal plants, natural products, CVD-related target proteins, docking results, diseases and clinical biomarkers has been developed (Gu *et al*., 2013b). This database is providing a research platform for bioactives from medicinal plants. Also a chemical botanicals library consisting of 389 botanicals having anti-infective and anti-inflammatory properties has been created (Ding *et al*., 2014). The potential of natural products to use as lead candidates for multi target cancer therapies has been demonstrated experimentally using network based multi target computational approach (Luo *et al*., 2014). Thus, network pharmacology approach is useful to understand complex relationships among bio actives, their molecular targets, diseases and mechanism of action (Berger and Iyengar, 2009; Cheng *et al*., 2012; Li *et al*., 2011).

In this way, possible mechanisms and rationale behind putative synergistic actions of traditional medicines can be understood with help of network pharmacology. Such studies have not yet been done on Ayurvedic formulations. We present here preliminary study of this emerging technique to explore potential applications of Ayurvedic formulation *Triphala*.

Example

Ayurvedic Formulation Triphala

We have constructed a pharmacology network of Triphala, which is one of the most popular and widely used Ayurvedic formulations. Triphala contain fruits of three myrobalans – *Emblica officinalis* (EO; Amalaki) also known as *Phyllanthus emblica; Terminalia bellerica* (TB; Vibhitaka) and *Terminalia chebula* (TC; Haritaki). Triphala is an efective medicine to balance all three *Dosha*. It is used as a general health promoter, for cosmetic purpose to improve skin and hair quality and for diabetic wound management. It is considered as a good rejuvenator *Rasayana*, which facilitates nourishment to all tissues or *Dhatu*.

Triphala is the drug of choice for the treatment of several diseases, especially those of metabolism, dental and skin conditions and treatment of cancer (Baliga, 2010). It has a very good effect on the health of heart, skin, eyes and helps delaying degenerative changes, such as cataracts (Gupta *et al*., 2010). Triphala can be used as inexpensive and non-toxic natural product for the prevention and treatment of diseases where vascular endothelial growth factor-A induced angiogenesis is involved (Lu *et al*., 2012). Recently, the beneficial role of Triphala in disease management of proliferative vitreoretinopathy has also been reported (Sivasankar *et al*., 2015). One of the key ingredients of Triphala is Amalaki. Some studies have already shown the beneficial effect of Amalaki Rasayana in suppressing neurodegeneration in fly models of Huntington's and Alzheimer's diseases (Dwivedi *et al*., 2012; Dwivedi *et al*., 2013).

Triphala can give multiple and diverse actions based on its composition, dose, dosage form and vehicle of administration (Fig. 1). The complex proportions of bioactives might have synergistic action and are possibly designed in a particular way in regulating underlying pathophysiological processes based on internal milieu. This hypothesis can be studied with the help of network pharmacology.

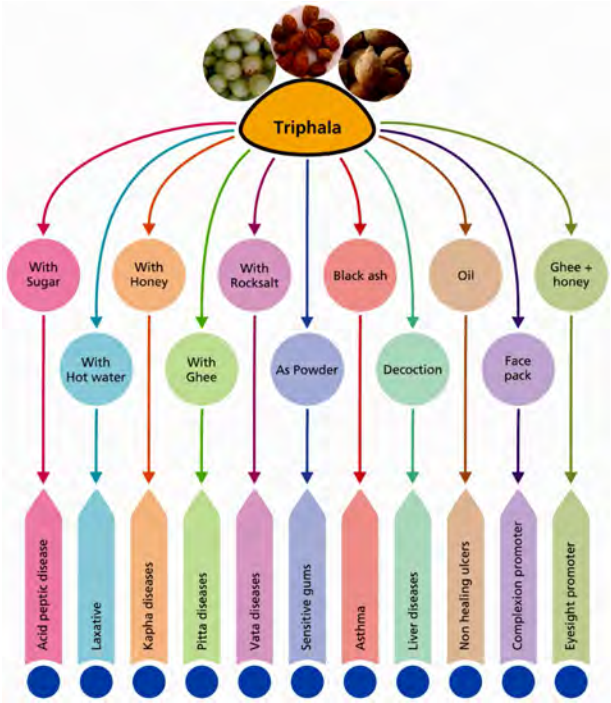

Fig. 1: Multidimensional Effects of Triphala. (Reproduced with permission from Patwardhan B, Mutalik G, Tillu G 2015. Integrative Approaches for Health. Elsevier)

Methods

Mining Bioactives

The bioactive compounds of the three myrobalans EO, TB and TC reported in literature were used in this study. The bioactives were retrieved from the Universal Natural Products Database (UNPD), which is designed to be a comprehensive resource of natural products for virtual screening. Presently, it comprises of 229,358 structures. The 3D structures of bioactives, which are freely accessible and available in the '.sdf' or 'mol2' formats (file structures to store spatial data) were used for the study (Gu *et al*., 2013a).

Predicting Targets and Associated Diseases

The '.sdf' files having structures of bioactives were submitted to the Binding database or 'Binding DB' (Liu *et al*., 2007) for predicting their target proteins. Binding DB focuses on interactions of proteins considered as candidate drug-targets with ligands that are small drug-like molecules. It predicts targets using structural similarity to the studied ligands, and scores the results according to closeness to the ligands, where 1 is the highest value. We have selected targets of those bioactives with a score ranging from 0.9 to 1. Binding DB is connected to numerous other databases, which were used to extract more information regarding the targets. The protein symbols were pulled out from UniProt (Bairoch *et al*., 2005) using the UniProt IDs given in Binding DB. The targets of the bioactives were searched for in the Therapeutic Targets Database (TTD) for their association with any disease or indication (Zhu *et al*., 2012). The structural similarity scores of the bioactives can be extrapolated and assigned to the interactions of the bioactives and their targets.

Network Construction

A network is made up of nodes, the points of communication or redistribution and edges, the lines of communication or relation joining the nodes. The entities that form the nodes of the networks include: Triphala and its constituent botanicals (EO, TB and TC), the bioactive compounds present in the constituent botanicals, the targets of the bioactives and the target related diseases. The networks were constructed using Cytoscape 3.2.0, a java based open source software platform for visualizing complex networks and integrating them with any type of attribute data (Shannon *et al*., 2003). The networks link the formulation to its botanical constituents, from the latter to their bioactives that in turn link to the targets of the bioactives and finally to diseases associated with the targets. Duplicate names of the bioactives, owing to presence of different conformations of the bioactive entries, were eliminated while constructing networks. The 'Network Analyzer' tool available in Cytoscape was used for analyzing the networks.

Results and Discussion

The botanicals of Triphala-EO, TB and TC are reported to contain 115, 30 and 52 bioactives respectively. Thus Triphala formulation as a whole contains 174 bioactives. The number of bioactives having interactions, equal to or greater than 0.9 (high scoring bioactives), for EO, TB, TC and Triphala are 38, 13, 22 and 55 respectively.

Analysis of the nodes and edges of the networks is given in Table 1. The nodes of networks representing three myrobalans (EO, TB and TC) and Triphala, their bioactives, targets of bioactives and the diseases associated with the targets are noted in the Table 1. The table also gives bioactives of botanicals that have maximum interactions with targets.

Table 1: Nodes and edges of EO, TB, TC and Triphala

	EO	TB	TC	Triphala
Bioactives	115	30	52	174
High scoring Bioactives	38	13	22	55
Targets	44	21	23	44
Diseases	78	46	48	78
Bioactive-target interactions	134	64	75	190
Highly interactive bioactives	KAE, QUE, EA	MOEA, DMEA, EA	PGG, TGG, DGG	KAE, QUE, MOEA, EA, DMEA

Network of EO shows that it contains 38 high scoring bioactives, which are involved in 78 diseases through 44 targets (Fig. 2A). The EO bioactives with highest number of interactions include Kaempferol (KAE), Quercetin (QUE) and Ellagic acid (EA).

Network of TB shows that it contains 13 high scoring bioactives, which are involved in 46 diseases through 21 targets (Fig. 2B). The TB bioactives with highest number of interactions include 3-methoxyellagic acid (MOEA), 3, 3'-dimethylellagic acid (DMEA) and EA.

Network of TC shows that it has 22 high scoring bioactives, which are involved in 48 diseases through 23 targets (Fig. 2C). The TC bioactives with highest number of interactions include 1, 2, 3, 4, 6-pentagalloylglucose (PGG), 1, 2, 3, 4, 6-tetra-O-galloyl-β-D-glucose (TGG) and 1, 6-digalloyl-β-D-glucopyranoside (DGG).

As a composite formulation, Triphala is involved in 78 diseases through 44 targets. All the 55 bioactives, their targets and their diseases are shown in Fig. 3. Triphala bioactives with highest number of interactions include KAE, QUE, MOEA, DMEA and EA. Seven high scoring bioactives are shared among the three botanicals EO, TB and TC. Only one high scoring bioactive is shared between TB and TC as well as between EO and TB, while TC and EO share two high scoring bioactives.

The number of targets and diseases for Triphala are more than that of the individual botanicals, indicating better disease coverage of the formulation. The targets and diseases of Triphala match with that of EO. However, the number of bioactive-target interactions are 190 for Triphala, which are much higher as compared to 134 for EO. Thus, there are more bioactives interacting with the same targets in Triphala. EO, TB, TC and Triphala have many targets

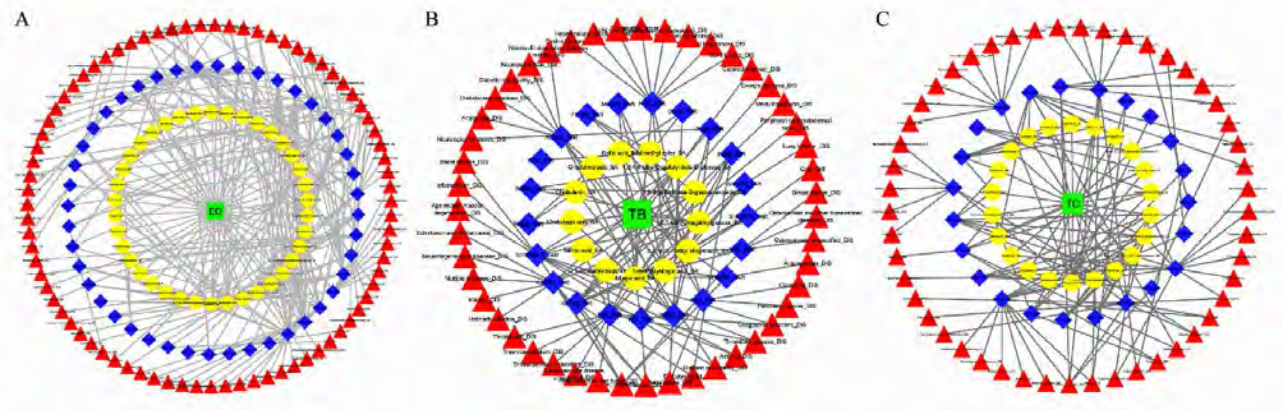

Fig. 2: Pharmacology Networks of A) *E. officinalis* (EO), B) *T. bellerica* (TB) *and* C) *T. chebula* (TC) which connect bioactives (yellow ellipses), targets (blue diamonds) and diseases (red triangles)

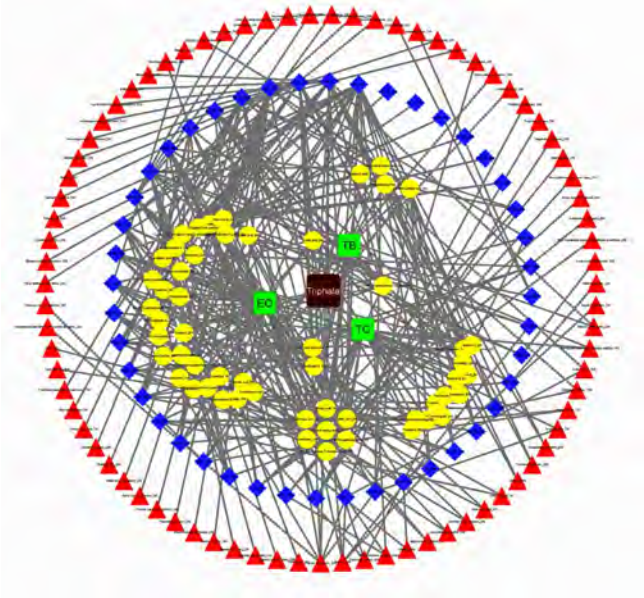

Fig. 3: Pharmacology Network of Triphala connecting three Myrobalans (green squares), Bioactives (yellow ellipses), Targets (blue diamonds) and Diseases (red triangles)

in common such as F10, SERPINE1, RGS7, GSTA1 and CA2. The reported bioactives from each botanical and Triphala that are interacting with these targets are given in Table 2. It is observed that targets like BACE1 are not common to all, but are present in Triphala. Our analysis indicates that Triphala has more bioactives interacting with the same targets as compared to individual botanicals. We hypothesize that the bioactives of Triphala have synergistic action in regulating their targets. We are planning further studies to test this hypothesis through validation involving suitable in vitro and in vivo experiments.

Applications for Drug Discovery

Our network pharmacology analysis indicates that classical formulations like Triphala can have therapeutic effects against a wide range of complex diseases, such as cardiovascular diseases, asthma, arthritis, diabetes and cancer. Following this approach, it is possible to develop pharmacology networks of many Ayurvedic formulations to know their rationale and scientific basis. Potential applications of network pharmacology are given in Table 3.

In this report our main objective is to show a

Table 2: Targets and bioactives interactions

Targets	Bioactives			
	EO	TB	TC	Triphala
F10	11	5	7	15
SERPINE1	9	3	5	11
RGS7	8	6	7	11
GSTA1	6	3	5	8
CA2	5	2	3	6
BACE1	1	0	7	8

Table 3: Potential Applications of Network Pharmacology

Ayurveda	· Biological understanding for use of Ayurvedic medicine
	· Understanding the rationale of traditional formulations
	· Interpretations of the mechanism of action of Ayurvedic medicines
	· Studying safety and efficacy of Ayurvedic medicines
	· Possible substitutes for endangered botanicals
Pharmacology	· Identifying 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 drug-drug interactions
Drug Research and Development	· Identifying novel drug targets
	· Reduced cost and time through *in silico* evaluation
	· Precise research questions for clinical studies
	· Understanding the signaling pathway of disease types
	· Designing experiments based on drugs and targets
	· Drug repurposing

proof of concept to explore potential applications of this emerging technique of network pharmacology. While this technique is very useful, we wish to acknowledge some limitations of our preliminary study. First, we have relied only on open source/open access databases, which may not have covered all reported bioactives and targets. Second, we have not done detailed relationships analysis.

Much more work is required to build verifiable data, supported by appropriate validation experiments. Studies are underway to explore how such networks can be useful in drug/formulation discovery and therapeutic management of specific diseases such as cancer and neurodegenerative diseases.

Conclusions

Network pharmacology can be a very useful tool to understand non-linear, complex relations between bioactives and underlying pathophysiological processes. It also provides a scientific platform for research on Ayurveda and other traditional medicines. Systematic analysis of pharmacological networks can give newer insights into rationale, indications and possible mechanisms of traditional medicines. Such analysis can also help in the identification of new targets and leads to address the present impasse in drug discovery. Network pharmacology can also open a new opportunity for moving towards intelligent formulation discovery combining strengths of traditional wisdom and modern science. We hope that Indian researchers will be able to use this emerging technique of constructing interactive pharmacology networks of Ayurvedic drugs to know their rationale, mechanisms and scientific basis.

Acknowledgement

We thank Savitribai Phule Pune University for facilities. U C thanks the University Grants Commission for Dr. D S Kothari Post Doctoral Fellowship. N M thanks Director IBB.

References

Bairoch A, Apweiler R, Wu C H, Barker W C, Boeckmann B, Ferro S, Gasteiger E, Huang H, Lopez R, Magrane M, Martin M J, Natale D A, O'Donovan C, Redaschi N and Yeh L S L (2005). The Universal Protein Resource (UniProt). *Nucleic Acids Res* **33D** 154-9

Baliga M S (2010). Triphala, Ayurvedic formulation for treating and preventing cancer: a review *J Altern Complement Med* **16** 1301-8

Berger S I and Iyengar R (2009). Network analyses in systems pharmacology. Bioinformatics. doi:10.1093/bioinformatics/btp465

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

Cho D Y, Kim Y A and Przytycka T M (2012). Chapter 5: Network biology approach to complex diseases *PLoS Comput Biol* **8** e1002820

Ding W, Gu J, Cao L, Li N, Ding G, Wang Z, Chen L, Xu X and Xiao W (2014). Traditional Chinese herbs as chemical resource library for drug discovery of anti-infective and anti-inflammatory *J Ethnopharmacol* **155** 589-598

Dwivedi V, Anandan E M, Mony R S, Muraleedharan T S, Valiathan M S, Mutsuddi M and Lakhotia S C (2012). In vivo effects of traditional Ayurvedic formulations in *Drosophila melanogaster* model relate with therapeutic applications *PLoS One* **7** e37113

Dwivedi V, Tripathi B K, Mutsuddi M and Lakhotia S C (2013). Ayurvedic Amalaki Rasayana and Rasa-Sindoor suppress neurodegeneration in fly models of Huntington's and Alzheimer's diseases *Curr Sci* **105** 1711-1723

Ellingson S R, Smith J C and Baudry J (2014). Polypharmacology and supercomputer-based docking: opportunities and challenges *Mol Simulations* **40** 848-854

Gu J, Gui Y, Chen L, Yuan G, Lu H Z and Xu X (2013a). Use of Natural Products as Chemical Library for Drug Discovery and Network Pharmacology *PLoS One* **8** e0062839

Gu J, Gui Y, Chen L, Yuan G and Xu X (2013b). CVDHD: a cardiovascular disease herbal database for drug discovery and network pharmacology *J Cheminform* **5** 51

Gupta R, Gabrielsen B and Ferguson S M (2005). Nature's medicines: traditional knowledge and intellectual property management. Case studies from the National Institutes of Health (NIH), USA *Curr Drug Discov Technol* **2** 203-219

Gupta S C, Patchva S and Aggarwal B B (2013). Therapeutic roles of curcumin: lessons learned from clinical trials *AAPS J* **15** 195-218

Gupta S K, Kalaiselvan V, Srivastava S and Agrawal S S (2010). Evaluation of anticataract potential of Triphala in selenite-induced cataract: *In vitro* and *in vivo* studies *J Ayurveda Integr Med* **1** 280-6

Hao D C and Xiao P G (2014). Network Pharmacology: A Rosetta Stone for Traditional Chinese Medicine *Drug Dev Res* **75** 299-312

Harvey A L (2008). Natural products in drug discovery. Drug Discov *Today* **13** 894-901

Holland B K (1994). Prospecting for drugs in ancient texts *Nature* **369** 702

Hopkins A (2007). Network pharmacology *Nat Biotechnol* **25** 1110

Hopkins A (2008). Network pharmacology: the next paradigm in drug discovery *Nat Chem Biol* **4** 682-90

Li J, Lu C, Jiang M, Niu X, Guo H, Li L, Bian Z, Lin N and Lu A (2012). Traditional chinese medicine-based network pharmacology could lead to new multicompound drug discovery Evidence-based Complement *Altern Med* e149762

Li S (2007). Framework and practice of network-based studies for Chinese herbal formula *J Chinese Integr Med* **5** 489-493

Li S and Zhang B (2013). Traditional Chinese medicine network pharmacology: theory, methodology and application *Chin J Nat Med* **11** 110-20

Li S, Zhang B and Zhang N (2011). Network target for screening synergistic drug combinations with application to traditional Chinese medicine. *BMC Syst Biol* **5** doi:10.118611752-05-09-5-61-10

Liu T, Lin Y, Wen X, Jorissen R N and Gilson M K (2007). BindingDB: A web-accessible database of experimentally determined protein-ligand binding affinities *Nucleic Acids Res* 35

Lu K, Chakroborty D, Sarkar C, Lu T, Xie Z, Liu Z and Basu S (2012). Triphala and Its Active Constituent Chebulinic Acid Are Natural Inhibitors of Vascular Endothelial Growth Factor-A Mediated Angiogenesis *PLoS One* **7** e43934

Luo F, Gu J, Chen L and Xu X (2014). Systems pharmacology strategies for anticancer drug discovery based on natural products *Mol Biosyst* **10** 1912-7

Patwardhan B (2014). Rediscovering Drug Discovery. Comb. Chem *Highthroughput Screen* **17** 2014

Patwardhan B and Mashelkar R A (2009). Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? *Drug Discov Today* **14** 804-11

Patwardhan B, Mutalik G and Tillu G (2015). Integrative Approaches for Health, Elsevier

Patwardhan B, Vaidya A D B and Chorghade M (2004). Ayurveda and natural products drug discovery *Curr Sci* **86** 789-799

Shannon P, Markiel A, Ozier O, Baliga N S, Wang J T, Ramage D, Amin N, Schwikowski B and Ideker T (2003). Cytoscape: A software Environment for integrated models of biomolecular interaction networks *Genome Res* **13** 2498-2504

Shi S H, Cai Y P, Cai X J, Zheng X Y, Cao D S, Ye F Q and Xiang Z (2014). A network pharmacology approach to understanding the mechanisms of action of traditional medicine: Bushenhuoxue formula for treatment of chronic kidney disease *PLoS One* **9** e0089123

Sivasankar S, Lavanya R, Brindha P and Angayarkanni N (2015). Aqueous and Alcoholic Extracts of Triphala and Their Active Compounds Chebulagic Acid and Chebulinic Acid Prevented Epithelial to Mesenchymal Transition in Retinal Pigment Epithelial Cells, by Inhibiting SMAD-3 Phosphorylation *PLoS One* **10** e0120512

Yang M, Cheng C, Yang J and Guo D (2012). Metabolite profiling and characterization for medicinal herbal remedies *Curr Drug Metab* **13** 535-557

Zhang Z, Li X, Lv W, Yang Y, Gao H, Yang J, Shen Y and Ning G (2008). Ginsenoside Re reduces insulin resistance through inhibition of c-Jun NH2-terminal kinase and nuclear factor-kappa *B Mol Endocrinol* **22** 186-195

Zhao N, Li J, Li L, Niu X Y, Jiang M, He X J, Bian Z X, Zhang G and Lu A P (2015). Molecular network-based analysis of Guizhi-Shaoyao-Zhimu decoction, a TCM herbal formula, for treatment of diabetic peripheral neuropathy *Acta Pharmacol Sin* (in Press)

Zhu F, Shi Z, Qin C, Tao L, Liu X, Xu F, Zhang L, Song Y, Liu X, Zhang J, Han B, Zhang P and Chen Y (2012). Therapeutic target database update 2012: A resource for facilitating target-oriented drug discovery *Nucleic Acids Res* **40** gkr797

Zimmermann G R, Lehár J and Keith C T (2007). Multi-target therapeutics: when the whole is greater than the sum of the parts *Drug Discov Today* **12** 34-42.