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Network Pharmacology and Traditional Chinese Medicine

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1. Introduction

Traditional Chinese medicine (TCM), an age-old healthcare system derived from China, is a mainstream medicine in China and is also popular in many other parts of the world [1-3]. Due to historic reasons, the scientific base of TCM awaits consolidation but emerging evidence has begun to illustrate TCM as an area of important medical rediscoveries. For example, the 2011 Lasker-DeBakey Clinical Medical Research Award was awarded to Youyou Tu for the discovery of Chinese herb-derived artemisinin, a drug for malaria that has saved millions of lives across the globe [4,5] and the 7th Annual Szent-Györgyi Prize was awarded to Zhen-Yi Wang and Zhu Chen for their TCM research that led to the successful development of a new therapeutic approach to acute promyelocytic leukaemia. These award-winning projects were both conducted well before the human genome was decoded and when information technology was in infancy. What has TCM to offer in the post-genomic era and the Information Age? To address this important question, the GP-TCM project kicked in as the 1st EU-funded EU-China collaboration dedicated to applying emerging technologies to TCM research [6,7]. Besides the consensus that omics and systems biology approaches will likely play major roles in addressing the complexity of TCM [7-9], more than half GP-TCM consortium members who responded to a consortium survey also cast votes of confidence in network pharmacology in TCM research [7]. Then, what is network pharmacology? What is the state of the art of this technology in modern pharmacological and toxicological studies, and finally, what are its possible roles in TCM research?

2. What is network pharmacology?

Network could be used to refer to any interconnected things or people in a virtual or actual net-like structure. For example, in information technology, anatomy, systems biology and

social science, it could refer to interconnect computers (e.g. intranet or internet), bodily structures (e.g. neurons and vessels), molecules (e.g. genes, mRNAs, proteins, metabolites), or an association of individuals having a common interest, formed to provide mutual assistance, helpful information, or the like (e.g. the FP7 GP-TCM consortium) [6,7], respectively. In network pharmacology, "network" doesn't mean that a group of scientists who share similar interests are interconnected, as the FP7 GP-TCM consortium and the famous Polymath Project of mathematicians do [7,10], nor does it refer to interconnected anatomical structures or computers. Instead, the concept is built on the belief that targeting multiple nodes in interconnected molecular systems, rather than individual molecules, could lead to better efficacy and fewer adverse effects [11,12]. It integrates polypharmacology [13,14] and computational pharmacology or *in silico* pharmacology [15] and is based on the principles and objectives of systems pharmacology [16,17]. Thus, network pharmacology could be regarded as the technical route to the ultimate ideal of systems pharmacology, in which drugs are designed to benefit a human being as an integrative system, taking into consideration the complex dynamics of interconnected organic and molecular systems.

In brief, network pharmacology is based on the principles of network theory and systems biology. Graph or network theory is a branch of mathematics, which is concerned with characteristics of networks ("webs") of interacting objects. Systems biology, as the name implies, deals with complex and comprehensive living systems involving a finite number of hierarchically ordered components, which form interacting networks affected by, and responding to, various perturbations within the system itself and from the environment [18]. Typical for the network's response to perturbations is the return of a system to a previous state or the adoption of a new homeostasis. 'Systems biology is an analytical approach to investigating relationships among system's components in order to understand its emergent, i.e. network-level properties' [19]. Emergent properties, e.g. homeostasis, are higher-level characteristics of complex systems, which are difficult to understand and predict just by studying a few components at a time in isolation. In medicine and pharmacology, when traditional approaches are mostly concerned with individual molecules or pathways, systems biology aims at integration of biological complexity at all levels of biological organisation, be it cell, organ, organism, or population.

Although polypharmacology and computational pharmacology have a relatively long history, network pharmacology and systems pharmacology are emerging new concepts that were only developed in the past 5-7 years. In October 2011, the Quantitative and Systems Pharmacology Working Group of the US National Institutes of Health published a white paper entitled *Quantitative and Systems Pharmacology in the Post-Genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms*, which provided a general report-level overview of the field from the perspectives of drug development and therapy and listed a number of important research goals for the future. It may be of interest to recapitulate one of the working definitions of the report:

"The goal of Quantitative and Systems Pharmacology is to understand, in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology."

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3. Principles of systems biology and network pharmacology

Detailed descriptions of principles of networks in systems biology can be found in several articles and reviews [20-22]. Herein, only a short presentation of the most important features is provided. Some most important characteristics and their biological examples are shown in Table 1. Network is formed by nodes (basic building blocks), their connections ('edges') and modules (a collection of nodes with a higher number of connections with each other in comparison with the rest of the network), and is characterised by a number of topological features defining relationships between network objects. There is a hierarchy in the properties of nodes in that some of them ("hubs") are more central with a high number of connections to other nodes whereas the majority of nodes have only one or a few connections at the most with other nodes. Bridging nodes connect two other nodes or modules in the network. As a consequence of non-random nature of biological networks, these networks are called "scale-free" in the network theory; Barabasi & Oltvai also referred to them as 'scale-rich' [21].

Network characteristics	Definition and explanation	Biological entities and functions (examples)
Node	Basic component interacting (pair-wise) with other node(s)	• Small-molecular substrates (metabolic network) •Genes (genetic regulatory network) •Proteins (protein-protein network)
Edge (link, connection)	Connection between two nodes	• Connection may be physical, regulatory, genetic interaction; • Metabolic network: enzyme-catalysed reactions • Genetic regulatory network: expression data
Node degree or connectivity	Number of links to other nodes; "hubs" are nodes with a large number of connections, but there are only a few of them in any network	•Associated with topological robustness of biological networks, i.e. small degree nodes are more "disposable" than hubs
Path length	The average separation between arbitrarily chosen nodes	• Proximal and distal nodes in a functional module
Clustering coefficient	A measure of grouping tendency of the nodes	• Points to a motif and/or module
Motif and motif clusters	Recurring, significant patterns of interconnections	• Elementary building blocks (sub-networks) of biological networks
Network module	A set of nodes with high internal connectivity	• Subunits of a protein complex; dynamic functional unit, e.g. metabolic pathway, signalling cascade
Bridging node	A node bridging the shortest path between two other nodes or modules within a network	• A node linking two functional units ("crosstalk" point; a potential drug target), etc.
Bridging centrality	Measure for connectivity within a network for the measured node	

Table 1. Important network characteristics in biological and pharmacological networks [18,19,21]

Complex networks possess characteristics that are of considerable importance for the investigation of drug discovery and drug treatment. Emergent properties of networks have already been mentioned earlier. Recently, there has been some theoretical and experimental work on strong and weak emergent features of networks [23]. Network robustness is a very important feature, which refers to the ability of a network to respond to external or internal perturbations [21]. Biological networks demonstrate remarkable robustness, which is at least partially based on a scale-free assembly: failure of nodes with few connections (small degree nodes), which form the majority of nodes, does not affect the integrity of the network, whereas failure of a few key hubs disintegrates the network. This latter phenomenon also is the basis of vulnerability of a network, if key hubs are targets of disruptive influences.

It is perhaps fair to mention and emphasise that many network-level emergent properties are important concepts in physiology, which is a system-level discipline. Concepts such as homeostasis, set-points, regulation, feedback control and redundancy have been in physiology for a long time to explain and model the interactions between cells, organs, systems and organisms [24]. Many of these system-level concepts have direct correspondences or relatives in network systems biology.

4. How to build a network?

Building a network involves two opposite approaches: a bottom-up approach on the basis of established biological knowledge and a top-down approach starting from the statistical analysis of available data [18]. In a more detailed level, there are several ways to build and illustrate a biological network [25]. Perhaps the most versatile and general way is the *de novo* assembly of a network from direct experimental or computational interactions, e.g. chemical/gene/protein screens. For the broad screening, the application of known interactions to an omic data set either manually or by using pathway-analysis software (Ingenuity Pathway Analysis, MetaCore, etc) has been widely used for hypothesis building and for identifying crucial network components. The most direct way to employ time-honoured modelling and simulation practices and more restricted and focused experimental datasets is by reverse engineering to generate a subset of networks *ab initio*. Most biochemical and regulatory pathways have been built in the past via painstaking experimental work on a single or a few components of a system, which has become understandable *in toto* only later in the research process. Likewise, it has to be realised that the first assembly of a network is just the beginning of an iterative modelling-simulation-experimentation cycle and the final outcome may be quite different from the original network.

Building a biologically relevant network needs a lot of relevant information. Indeed, emergence of systems biology and network analysis has occurred alongside with, and made possible to a considerable extent by, the developments in various omic technologies, high-throughput platforms, high-content screens, bioinformatics, and large-scale data handling and storage [26]. Production of data on genes (genomics), transcripts (transcriptomics), proteins (proteomics), epigenetic changes, metabolites (metabolomics) has put forth the neces-

sary raw material for building networks which encompass biologically relevant nodes (genes, proteins, metabolites), their connections (biochemical, regulatory), and modules (pathways, functional units), which through iterative process can become an increasingly relevant representation of real biological phenomena. On the other hand, the network analysis, once developed to a sufficient extent, offers a framework for data inclusion and interpretation by incorporating all pieces of information coming from earlier studies, current omics, high-content and high-throughput screening experiments, expected or unspecific findings, and these interpretations may lead to new experimental designs, both virtual and real.

Some experts envisage as a final goal the building of a virtual or *in silico* human [23]. Actually leading systems biologists signed the so-called Tokyo declaration in February 2008, with the aim for an *in silico* replica of a whole human body to be 90% complete by 2038. At the present, there are quite a number of simulation packages as spatiotemporal representations of various cellular functions [18].

5. Diseases as perturbations in biological networks

Many diseases, especially chronic ones, are initiated and perpetrated via dysregulation of multiple pathways, even if the primary reason is the mutation in a central gene associated with an endogenous or exogenous insult. The application of network analysis on human diseases, especially on those associated with polymorphisms, but increasingly also on diseases not primarily associated with structural mutations, has made it increasingly clear that chronic diseases demonstrate changes in expression of a large number of genes, proteins and metabolites, involve a large number of modules or functional units and show considerable overlap of important genes and network modules [27-31]. Obvious implications of this complexity are that single-target drugs may be completely inadequate to remedy a complex situation, and efficiency of any drug could be highly dependent on importance (centrality) of the target ("node" or "edge") in the disease network. In this respect, studies on drug-target networks suggest that many drugs developed earlier have rather peripheral targets in the disease-associated networks whereas many more novel drugs are interacting with targets closer to disease aetiology-linked components [32].

6. How to use network pharmacology in drug development?

Since the beginning of the genomic era, drug discovery process turned towards target based approaches for a deceptively simple reason: an ever efficient identification of a large number of potential targets for small and large molecules by the application of molecular biological and pharmacogenomics tools. Expectations have been large, but still costs have increased and the number of new medicinal entities stalled or decreased. Variable reasons for the increasing costs and a huge attrition even during clinical trials have been suggested, but many experts have begun to claim that the currently popular target-based approach is basically

flawed as a guide for drug discovery process. Instead, many authors have argued that systems biology and polypharmacology encompassing network thinking should be adopted to remedy the current difficulties in drug discovery and development. However, because network pharmacology is a relatively new concept, there is not too much robust data to demonstrate its superiority in drug development process. Yet some pieces of information seem to point out that indeed network pharmacology is providing a new paradigm [12,33]. Some of the current suggestions based on network pharmacology are compiled in Table 2.

Target	Rationale	Example
Molecular target identification	Magic bullet aimed at target; if a target is a hub, the consequence may be too much toxicity	Current paradigm
Edgetic perturbation	Drug targeting towards a certain edge (connection) of an intended target	Inherited disorders seem to separate into node removal and edgetic-specific variants [34]
Motifs, modules	Drug targeting towards a common feature or a functional unit of importance to disease (symptom or aetiology)	Inhibitors of protein kinases with common structural motifs in the active site
Bridging nodes	A target resulting in a modulation of crosstalk between nodules, but not vital to cell function	No good example
Multi-targets	Multiple disease-associated nodes, which can be affected in an optimal manner without compromising vital cellular functions	Anti-psychotics on multiple transmitter-associated receptors

Table 2. Drug design, discovery, and repurposing potentialities of network pharmacology

Recently, Swinney & Anthony analysed preclinical discovery strategies that were used to identify potential drug candidates, which were ultimately approved by the US Food and Drug Administration (FDA) between 1999 and 2008 [35]. They classified strategies to target-based screening, phenotypic screening, modification of natural substances and biologic-based approaches, with an additional consideration on molecular mechanisms of action (MMOA). Out of the 259 agents that were approved, 75 were first-in-class drugs with new MMOAs, and out of these, 50 (67%) were small molecules and 25 (33%) were biologics. They claimed that the contribution of phenotypic screening to the discovery of first-in-class small-molecule drugs exceeded that of target-based approaches — with 28 and 17 of these drugs coming from the two approaches, respectively — in an era when the major focus was on target-based approaches. They postulated that a target-centric approach for first-in-class drugs, without consideration of an optimal MMOA, might contribute to the current high attrition rates and low productivity in pharmaceutical research and development. Instead, among follow-on drugs a vast majority were the outcomes of target-based approaches, which seem rather natural considering that for these drugs mechanism of action and many other crucial pieces of information could come much earlier and in more useful manner than for the first-

in-class drugs. Actually the analysis of Swinney & Anthony concurs in many ways to the findings of Yildirim et al [32], in that many recent new drugs are interacting with novel targets thought to be more central in a corresponding disease aetiology, whereas follow-on molecules tend to stick to well-known, often more peripheral targets, which are more distal from core components of disease networks.

Although Swinney & Anthony did not specially mention network pharmacology (or corresponding) in their analysis, they refer to many crucial papers on network pharmacology. In their analysis phenotypic screening means the use of functional assays, which usually inform physiological parameters closer to real-life *in vivo* goals of drug therapy. Functional assays associated with the elucidation of the molecular mechanisms of action are much closer to the network analysis than the target-based screening. Intuitively it seems clear that functional assays are superior, at least from the drug discovery and development point of view, than target-based assays. However, in reality target-centred thinking has been dominant for more than a decade.

7. Properties of currently used drugs: Polypharmacology meets network pharmacology

Even if the current paradigm has been 'one target (or disease/symptom)-one drug', practising pharmacologists have always known that practically all drugs have multiple effects based on various known or unknown mechanisms, some desirable and others indifferent or harmful. A very good example is anti-psychotic drugs interacting with a large number of receptors and other targets. One target-one drug paradigm created a vision of a "magic bullet", which was eagerly adopted, although some scientists pointed out that even such "magic bullets" have pharmacokinetics-associated problems, e.g. potential drug-drug interactions, as well as structure-related problems such as allergic reactions. Now it is becoming increasingly apparent that biological systems are complex, redundant, homeostatic and resilient to perturbations and, consequently, most diseases are exhibiting much wider perturbations and variations than once thought. A new discipline, termed loosely as polypharmacology, has been gaining ground both conceptually and experimentally.

It seems highly likely that most current drugs are interacting with multiple targets. Current drug-protein interaction and chemogenomic studies have indicated that many drugs are interacting with two or more targets at reasonably close affinities. In these studies especially, the database of the FDA-approved drugs and their targets (effects) have been employed to create networks of drug-protein interactions [32,36] or to model similarities in chemical structure between drugs and potential ligands for the prediction of drug-target interactions [12, 37-38]. In Figure 1, a general approach to make use of the polypharmacology network is outlined [11]. In this approach the polypharmacology network is mapped onto the biological network, for example human disease-gene network, to reveal multiple actions of drugs on multiple targets and multiple diseases [30].

However, most of the studies on polypharmacology are based on computational and statistical associations, although some of the major findings have been studied further experimentally [37,38]. For example, a recent study demonstrated that unknown and unexpected "off-target" effects of many marketed drugs can be predicted by the computational analysis of ligand-target interaction; some predictions were experimentally confirmed [39]. Especially chemogenomic and chemoproteomic studies are based on direct or calculated affinities. It should be pointed out that affinity is not a reaction or other immediate outcome, e.g. antagonism, of an interaction and more distal functional or physiological consequences may or may not occur for various reasons even if a primary interaction has been demonstrated or predicted. Still clear evidence on functional consequences is required to be sure that an actual pharmacological significance is demonstrated for a substance.
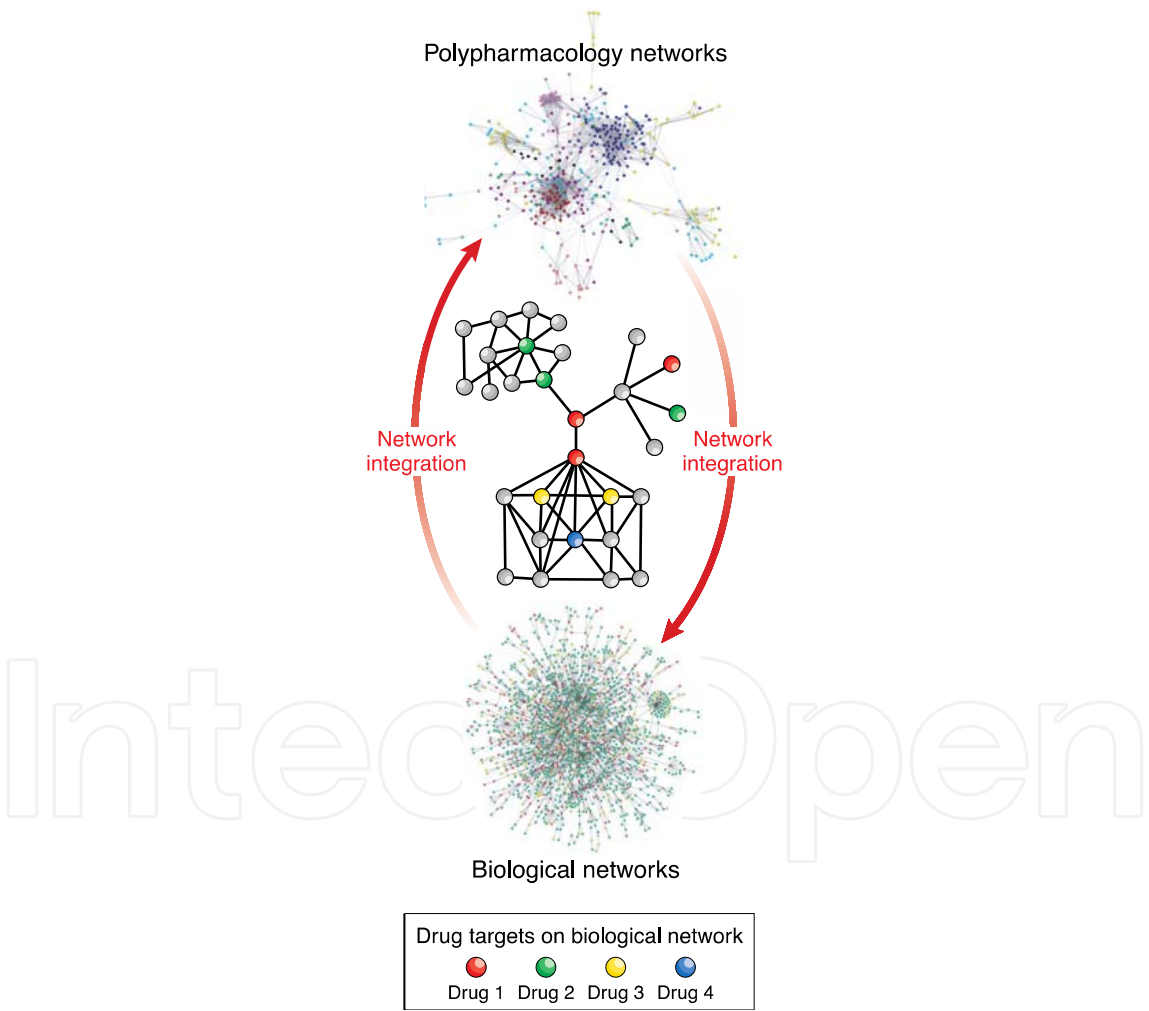

Figure 1. A network-centric view of drug action. Primary building blocks of network pharmacology are the drug-target network (above) and the biological network (below). The network in the centre is a part of the biological network in which proteins (nodes) targeted by the same drug are represented in the same colour. Consequently drug efficacy and toxicity can be understood by action at specific nodes and hubs. For the definition of nodes and hubs, see Table 1. The figure is reprinted by permission from Macmillan Publishers Ltd: [Nature Biotechnology] (11), copyright (2007).

Recently, a polypharmacological approach has been extended to include functional considerations. Simon et al [40] employed 1177 FDA-approved small molecular drugs by investigating interaction profiles based on *in silico* docking/scoring methods to a series of virtual non-target protein binding sites and contrasting these profiles with 177 major drug categories of the same series of FDA-approved drugs. Statistical analyses confirmed a close relationship between the studied effect categories and interaction profiles of small molecule drugs. On the basis of this relationship, the comprehensive effect profiles of drugs were apparent and furthermore, effects not previously associated with particular drugs could be predicted. A rather curious finding – which is not easily explained by classical pharmacological concepts – was that the prediction power was independent of the composition of the protein set used for interaction profile generation. Perhaps general chemical and physicochemical properties of molecules are of importance for potential interactions in general, whereas pharmacophores, i.e. specific stereochemical groups, are crucial for specific high-affinity interactions.

8. Systems toxicology

Network approach helps to understand and reveal on-target and off-target toxicity of pharmaceuticals, but it also helps to delineate the toxicities of any chemicals, be they industrial chemicals, agrochemicals, cosmetics, environmental pollutants, etc. Omic approaches provide voluminous information about time-dependent changes at various levels of biological complexity after the administration of a chemical and provide the so-called signatures of toxicity. On the other hand, the application of known and characterised toxicants has delineated a finite number of pathways of toxicity. Bringing this information together at the established network and systems level would create a 'systems toxicology' approach, analogous to systems pharmacology and polypharmacology [41].

9. Physiologically based pharmacokinetic (PBPK) modelling

A relatively isolated area in pharmacology and toxicology is the model building to describe the behaviour and disposition of drugs and other chemicals in the body [42]. Especially those models that make use of physiological principles resemble in many ways network pharmacology. Whole body PBPK models consist of absorption sites and manners, tissues with membranes drugs and their metabolites have to cross, with special reference to tissues which metabolise and excrete drugs and their metabolites, and so on. Concentrations of a studied chemical (and its important metabolites) in these various compartments could be equated to nodes. Connections are permeation and corresponding constants (for passive and active processes in the membranes and other cellular barriers, distribution coefficients, enzymatic reactions (clearance), and so on. Although the number of building blocks in pharmacokinetic models is finite and certainly much less than in most systems pharmacology networks, models have become quite complex, but still useful for predicting the behaviour

of a drug in the body under various circumstances. Efforts to link PBPK models with *in vitro-in vivo* extrapolations under the systems pharmacology umbrella are underway [43].

Whole-body PBPK models illustrate also important challenges to, and potentialities of, network pharmacology. First of all, the framework for modelling is multi-scale [44], starting from enzymes and transporters (dealing with transformation and movement of drugs) and their quantitative functions (clearance, metabolite formation, membrane penetration) and their regulation and functions in the cells and tissues, kinetics of drugs and their metabolites throughout the body via circulation, distribution to different organs, elimination in urine, in bile, and integration of all processes into a dynamic model representing an individual (*in silico* human or animal, for that matter) and extending the modelling to evolution, development, environment, populations, diseases, etc. PBPK modelling is increasingly used in drug development and toxicity risk assessment with considerable success, probably because it is a rather restricted in dealing with behaviour of a single substance in the framework of a finite number of active players. On the other hand, pharmacodynamic models that have been developed for at least a couple of decades are closer to network building (*ab initio* models).

10. TCM network pharmacology & "network targets" for TCM drugs

In 2010, Liu & Du raised the concept of "TCM network pharmacology", linking the multiple components that play principal, complementary and assistant therapeutic roles in TCM formulae to principal, complementary and assistant targets in a disease network. They believed that such an approach to projecting a TCM drug component network onto a disease network offers a novel philosophical guide and technological route to designing and understanding mechanisms of action of TCM drugs and is thus likely proven important in modernisation of TCM [45]. Similarly, Li emphasised "network targets" of systems, connectivity and predictiveness features in studying TCM formulae and syndromes and the work of his team showed that the "network target" approach could facilitate discovery of effective compounds, understanding their interrelation, elucidating relationship between TCM formulae and diseases or TCM syndrome, developing rational TCM drug, as well as guiding integrated use of TCM and conventional drugs [46].

TCM network pharmacology heavily relies on omic platforms as well as algorithm- and network-based computational tools, which are elegantly summarised most recently by Leung et al [47]. In addition, TCM network pharmacology heavily relies on ever updating omics, pharmacological and TCM-related databases. While concerns about duplication of efforts, poor standardisation and low sustainability remain, many TCM databases have been developed, as recently reviewed by Barlow et al [48]. To mention a few, the Chem-TCM database developed by King's College London [49] has now been commercialised by TimTec LLC (http://www.chemtcm.com); the trial version of World Traditional & Natural Medicine Patent Database is currently being developed by Beijing East Linden Co. Ltd (http://www.east-linden.net/NewsShow.aspx?news_id=20081127102018850246); and the Herbal Ingredient Target database (HIT: http://lifecenter.sgst.cn/hit/) and the TCM Information Database

(TCM-ID: http://tcm.cz3.nus.edu.sg/group/tcm-id/tcmid_ns.asp) have been developed by academics based in China and Singapore [50,51].

11. Applications of TCM network pharmacology

In TCM, formulae are usually prescribed based on TCM syndrome patterns of a given patient, rather than a disease as defined in Western medicine. Thus, an important part of TCM network pharmacology is to establish links between network molecular targets and TCM syndrome patterns. Ma et al surveyed 4575 cases of Cold Syndrome patients and examined gene expression information of a typical Cold Syndrome pedigree by microarray. Results indicated that Cold Syndrome related genes played an essential role in energy metabolism, which were tightly correlated with the genes of neurotransmitters, hormones and cytokines in the neuro-endocrine-immune interaction network [52]. In TCM clinics, Cold Syndrome is treated by Warm formulae and Hot Syndrome is often treated by Cold formulae. Identification of the gene networks of Cold and Hot Syndromes [52, 53-55] should help understand nature of a condition and unravel mechanisms of its related TCM treatment [56].

In addition, Wang and colleagues (2011) proposed that network pharmacology could be applied to the following aspects of TCM studies:

11.1. "Disease-gene-target" network-based studies to identify targets and pathways affected by TCM drugs and to obtain fuller pictures of the efficacy and mechanisms of action of TCM drugs

Sun et al performed bioinformatic analysis of anti-Alzheimer's herbal medicines and found that ingredients of anti-Alzheimer's herbs not only bound symptom-relieving targets, but also interact closely with a variety of successful therapeutic targets related to other diseases, such as inflammation, cancer and diabetes, suggesting the possible cross-talk between these complicated diseases. Furthermore, the anti-Alzheimer's herbal ingredients densely targeted pathways of Ca^{2+} equilibrium maintaining upstream of cell proliferation and inflammation [57].

Wen et al used microarray and network analysis to establish that Si-Wu-Tang is an Nrf2 activator and phytoestrogen, thus suggesting its use as a nontoxic chemopreventive agent [58]. In fact, network analysis of all sorts of omic data can be used to explore the molecular targets and mechanisms of action of TCM drugs [59,60], as recently reviewed by Buriani et al [8]. In network pharmacology, roles for functional genes and proteins might vary in different stages of the same disease, thus the same disease could be treated differently, as emphasised in TCM; on the other hand, some functional proteins are "hubs" in the disease networks of more than one disease, thus different diseases could be treated similarly by targeting the same hubs [45]. Based on gene and phenotype information associated with the ingredient herbs of the classical Liu-wei-di-huang (LWDH) formula and LWDH-treated diseases, it was found that LWDH-treated diseases showed high phenotype similarity and identified certain "co-modules" enriched in cancer pathways and neuro-endocrine-immune

pathways, which may be responsible for the action of treating different diseases by the same LWDH formula [61].

11.2. Construction of "TCM drugs-targets-diseases" network and elucidation of the scientific base of TCM drug formulation through network analysis

Zheng et al studied the interactions between 514 compounds contained in a Chinese herbal formula Jingzhi Tougu Xiaotong Granule (JZTGXTG) and 35 drug targets of relevance to osteoarthritis and the distribution of 514 compounds in drug-target space. By analysing parameters of the JZTGXTG compound-target interaction network and the drug-target interaction network including network heterogeneity and characteristic path length, the results illustrated the possible molecular mechanisms of JZTGXTG in the prevention and treatment of osteoarthritis at the network pharmacology level [62].

To predict multi-targets by multi-compounds found in Aconiti Lateralis Radix Praeparata, Wu et al constructed the corresponding multi-compound-multi-target network based on the drug-target relationship of FDA approved drugs. The predicted targets of 22 compounds of Aconiti Lateralis Radix Praeparata were validated by literature. Each compound in the established network was correlated with 16.3 targets on average, while each target was correlated with 4.77 compounds on average, which reflected the "multi-compound and multi-target" characteristic of TCM drugs [63].

A "network target" approach has been applied to virtual screening and established an algorithm known as network target-based identification of multicomponent synergy (NIMS) to prioritise synergistic combinations of agents in a high-throughput manner [64]. From a "network target" perspective, a method called distance-based mutual information model (DMIM) was established to identify useful relations among herbs in numerous herbal formulae and a novel concept of "co-module" across herb-biomolecule-disease multilayer networks was proposed to explore the potential mechanisms of herbal formulations [61]. DMIM, when used for retrieving herb pairs, achieved a good balance among the herb's frequency, independence, and distance in herbal formulae. A herb network constructed by DMIM from 3865 collaterals-related herbal formulae not only recovered traditionally defined herb pairs and formulae, but also generated novel anti-angiogenic herb ingredients and herb pairs with synergistic or antagonistic effects [61].

Li et al constructed a network of nine major active compounds from Fufang Danshen formula, their multi-targets and multiple related diseases. The nine compounds were tanshinone II A, salvianolic acid B, protocatechuic aldehyde, danshensu, cryptotanshinone, notoginsenoside R1, ginsenoside Rg1, ginsenoside Rb1 and borneol. Network analysis showed that these compounds could modulate 42 genes associated with cardiovascular diseases (e.g. PPARG, ACE, KCNJ11, KCNQ1 and ABCC8), which were related to 30 clinical conditions, including non-insulin-dependent diabetes mellitus, hyperinsulinaemic hypoglycaemia, hypertension and coronary heart disease [65].

11.3. Building "TCM drug properties-clinical indications-adverse effects" networks and illustrating the relationship between TCM drug properties and efficacy

Jia et al analysed 117 drug combinations and identified general and specific modes of action and highlighted the potential value of molecular interaction profiles in the discovery of novel multicomponent therapies [66].

Zhu et al performed network analysis of 2215 chemicals identified in 62 Chinese herbs indicated for patients with chronic kidney diseases, including 836 chemicals contained in 22 tonifying herbs and 1379 chemicals contained in 40 evil-expelling herbs, according to TCM theory, in comparison with 99 drugs used in conventional medicine. Interaction networks of tonifying herbs, evil-expelling herbs and drugs showed different patterns, regarding network parameters, especially network degree, average number of neighbours and characteristic path lengths and shortest paths [67].

Wu et al constructed a relational network of TCM decoction slices to discover and interpret the correlations between the natures and functions of decoction slices and their clinically indicated symptoms and channel tropism as defined in TCM. 3016 pairs of decoction slice-symptom correlation associated with 646 decoction slices were discovered [68].

11.4. Evaluation of the safety, efficacy and stability of TCM products through constructing network models and network analysis

Emerging studies have supported the potential for network pharmacology in quality control of TCM drugs [69], which can well interpret the mechanisms of action of TCM drugs [70], help understand how different constituents of a TCM formulation and how TCM and chemical drugs synergised through targeting different nodes in disease-related networks [71,72]. There is no regulatory requirement of omics-based data in any submitted dossier to any regulatory agency, including for TCM products. However, it has been acknowledged that such studies are being increasingly performed, and almost surely will eventually be included into regulatory submission dossiers, possibly initially as supplementary materials [9]. Such a prospect is likely also shared with systems and network pharmacology.

12. Inspirations and challenges that TCM has to offer to network pharmacology

12.1. More networks

In network pharmacology, "network" refers to the molecular network in a targeted organism, for instance the "network targets" in patients. In TCM network pharmacology, however, complex TCM drugs themselves become another important molecular network, which might be called "network bullets" that interact with "network targets" in order to help the body to regain balance. Importantly, some components of TCM drugs are not to target "network targets", but to target other drug components, so as to alleviate their side-effects, im-

prove activity of the principal drug component, improve absorption and/or facilitate delivery of the principal drug to the targeted disease areas. Thus, TCM network pharmacology involves at least two networks to be considered in modelling and analysis.

In TCM, as guided by TCM theories, it is of paramount importance to choose a number of herbs (sometimes also zoological or mineral components) based on particular symptoms and characteristics of a patient. To assemble a formula or *fangji*, principal and enabling herbs are combined in order to optimise the effectiveness and minimise adverse effects. The principal herbs are known as the *jun* herbs, which treat the main cause or primary symptoms of a disease. The enabling herbs include the *chen* herbs, which serve to augment or broaden the effects of *jun* herbs and to relieve secondary symptoms; *zuo* herbs, which modulate the effects of *jun* and *chen* herbs and to counteract the toxic or side effects of these herbs; and the *shi* herbs, which function to facilitate absorption and delivery of active herbal components to the target organs. Thus, the combination of principal (*Jun*) and enabling (*Chen*, *Zuo* and/or *Shi*) components to form a drug network could form the basis for designing novel "network bullets" in the future application of network pharmacology.

12.2. More holistic

Network pharmacology aims to research and develop drugs holistically. However, the current model of network pharmacology that focuses on psychological and somatic diseases separately could be improved if it is to meet requirements of the psychosomatic model of health and ailments. Specifically, in addition to the well-known placebo effects of any interventions, the pathological damage of emotions to the internal organs is of primary concern of TCM practitioners. We propose that psychosomatic factors should be linked up in the next generation of network pharmacology and emotions should be included in the equations of future network analysis. By doing so, research might eventually help unravel and harness placebo effects and tackle psychosomatic ailments in a network pharmacological perspective.

12.3. More individualised

Personalised medicine is gaining momentum [73-75]. Network pharmacology needs to catch up with this trend as well. In TCM, individualisation goes beyond personalisation, because the same person at different ages, on different diets or living style, under different weather condition and at the different phases of the same disease could be diagnosed and treated differently. Can network pharmacology not only be personalised but also individualised, taking all the above variations into account?

13. Conclusions and perspectives

According to Paul Unschuld, a renowned German sinologist, cultural background has a great impact on the preferred directions of medical science. For example, both in ancient Greece and China philosophers came up with the idea of "relationist science" or "science of systematic correspondences" on the one hand and "analytical science" on the other. While in

ancient Europe relationist science was soon marginalised and analytical science became the approach of choice, in ancient China the beginnings of an analytical perspective were not pursued further and relationist science became the approach of choice [76]. Nowadays, the post-genomic era is characterised by globalisation and digitalisation. While omic data represent the state of the art of the analytical power of Western science, these data could be meaningless "sacs of data" unless they are linked up functionally using a relationist approach. At this point, the dominant approaches in the West and East are integrated to relate pieces of fragmented omic data and their functions and this might well serve as a bridge of both medical traditions. Analyses of state-of-the-art modern and TCM pharmacological and toxicological research data appear to support the concept of network pharmacology, i.e. a systems network-based model can help better understand health, disease and how Western medicine, TCM drugs or integrated TCM and Western medicine work. It can be expected that this approach could play a more important role in research and development of new drugs and in helping understand the mechanisms of action of drugs, especially in TCM.

Acknowledgements

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