## PERSPECTIVE

# The challenges and opportunities of traditional Chinese medicines against COVID-19: a way out from a network perspective

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The purpose of this perspective is to provide insights into the current challenges and opportunities of applying network pharmacology (NP) to illustrate the effectiveness of traditional Chinese medicines (TCMs) against the coronavirus disease 2019 (COVID-19). Emerging studies have indicated that the progression of COVID-19 is associated with hematologic and immunologic responses in patients, and TCMs may fight against COVID-19 regarding the two aspects. However, the underlying mechanisms remain largely unclear [1]. This perspective is intended as a brief report derived from our previous experience in investigating the efficacy of TCMs, via conventional reductionism-based research methods, holistic NP, systems biology, or "omics" research, and prevailing big data analysis.

The main idea of this perspective is outlined in Fig. 1.

The widespread and long-lasting pandemic has caused tens of millions of human lives infected and more than one million claimed. Although self-quarantine and the roll-out of vaccines as biological shields have effectively slowed down the COVID-19 infection rate, therapeutic strategies for COVID-19 must still be discovered. Several attempts have been made to treat COVID-19, directly by inhibiting or killing the coronavirus SARS-COV-2, as artemisinin does the plasmodium, or indirectly by preventing virus-induced complications. From the perspective of drug development, it is of importance to better understand the pathogenesis and delineated risk factor of COVID-19. Several studies have suggested that the COVID-19 is possibly impacted by the conditions of dysregulated immune systems or hypercoagulable states [2, 3]. This dysfunction may further cause immuno-thrombosis which is the symptom of deep vein thrombosis and multiple thrombi in the vessels of lungs, kidneys, or other organs. Immunothrombosis has been found as one of the major causes of death due to COVID-19 [4–6].

The coagulation pathways have long been regarded as separate entities from pathways that regulate innate immune responses to infections. However, it has been indicated that a remarkable degree of interplay exists between the immune and the coagulation systems [7], both of which involve complicated molecular mechanisms. Our previous network-based investigation also suggested that the protein targets involved in thrombosis pathways are highly associated with neuroactive−immune−metabolism/endocrine regulation [8]. With regard to COVID-19, a closer interaction between coagulation and immune system dysfunction may be one of the causes of death due to this disease.

According to "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia" in China [9], TCMs have been recommended, and the use of TCMs for COVID-19 treatment has achieved satisfactory effects [10, 11]. TCMs possibly act by preventing thrombosis and regulating the immune systems. Although these TCM therapies have achieved promising results, their exact mechanisms are restricted by explanations derived from reductionist methodologies, which focus on "one drug–one target". To this end, the presented "multi drug–multi target" therapeutic action mode inspires a new analytical approach by using networks to investigate TCMs. Such an approach is based on a schematic representation of the interactions among various entities. Additionally, owing to the rapid development of bioinformatics, NP, which combines network analysis and bioinformatics tools with polypharmacology, allows the illustration of TCMs comprehensively at the interactome levels.

In recent years, NP analysis has gained impetus as a powerful tool for understanding TCMs, as well as a novel paradigm for promoting TCM-based drug discovery. Various research models have been developed and applied in the past decade. A brief review of NP-based research on TCMs summarized the major types of network models that have been applied, including protein–protein interaction networks, pathway/signaling transduction networks, herb–herb interaction networks, and multi-layer networks [12]. As one of the most widely used models, multi-layer networks involve the depiction/visualization of multiple levels of interactions among herbs, compounds (ingredients), targets, pathways (bioprocesses), and diseases (functions, or effects). This model has sometimes been supplemented with network topological analysis. These pioneering explorations have paved the way for NP-based research on TCMs. However, this endeavor is replete with challenges, which mainly derive from the insufficiency of data. The insufficiency of data can greatly affect the accuracy of

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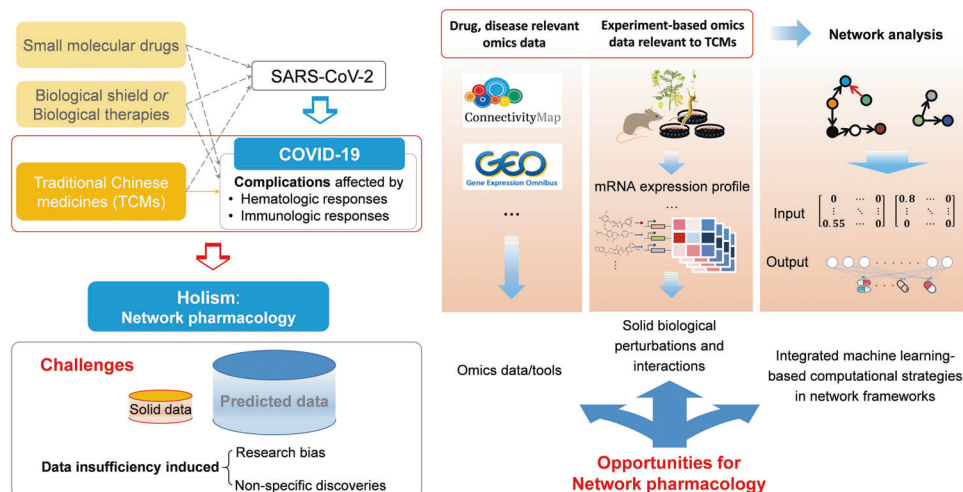HL Zuo et al.

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**Fig. 1 Framework.** Challenges and opportunities for network pharmacology-based research on traditional Chinese medicines against COVID-19.

the results when using multi-level interaction networks, and introduce research bias. Moreover, this situation would be further aggravated when experimental validation is overlooked. The insufficiency of data can be caused either by the lack of validated target information of compounds or the inconclusive corresponding target information predicted in most cases. For instance, in our previous study on Yu Ping Feng decoction, which is composed of Astragali Radix (Huangqi), Atractylodis Macrocephalae Rhizoma (Baizhu), and Saposhnikoviae Radix (Fangfeng), the targets of potentially active compounds were either rarely identified from the literature or rarely predicted by computational ligand-based approaches (chemical similarity search, or pharmacophore model), then, the undiscovered target of these potential active compounds, including astragalosides in Huangqi, atractylenolides in Baizhu, and part of the volatile components in Fangfeng, made their value has to be neglected in subsequent research.

Besides, the target profiles of different herbal ingredients predicted by either computational ligand-based approaches or receptor-based methods (e.g. reverse molecular docking) share much in common. Alternatively, it could be understood as a high amount of predicted "targets" of each herb in a relatively small target pool ("druggable genome") of these predicting methodologies (The "druggable genome" is a subset of only ~3000 genes in the human genome that contain the information needed to synthesize certain proteins. These proteins are normally capable of binding to drugs or potential active molecules. Although there are ~30,000 protein-coding genes in the human genome, only a few of them have been intensively studied). Then it was made that the functional enrichment analysis based on gene annotation or target annotation, tending to present the most common pathways or bioprocesses that many herbs might interfere with, even though they have very different therapeutic effects. This has been demonstrated in our previous research on Salviae miltiorrhizae radix et rhizoma (Danshen, DS) and Chuanxiong Rhizome (Chuanxiong, CX). These herbs are frequently used in clinical practice against thrombotic events. It was found that DS and CX share nearly 38% of common targets and over 90% of common pathways, although their similarity in compounds is less than 1%. Owing to the lack of experimental verification of compound–target interactions, determining the typical bioprocesses that DS or CX interferes with individually is difficult, that is, nonspecific results might be obtained. However, when studying TCMs, the "art of the diversity" is more important than the "art of the similarity", because

each single herb displays unique properties and activities to balance the human body.

TCMs are difficult to be illustrated, both reductively and holistically. Nevertheless, we are confident in the therapeutic potential that TCMs possess, and we have been focusing on realizing this potential. Although NP bears the promise of illuminating TCMs, it cannot adequately capture the entire chemical or therapeutic complexity of TCMs and the biological complexity of diseases without a data foundation. That is, the NP-based investigations of TCMs against COVID-19, induced by a novel coronavirus, might be hindered by the defects in data.

Overall, a primary challenge of NP analysis of TCMs against COVID-19 is the need to establish reliable associations among COVID-19, perturbed targets or pathways, and effective TCMs that target immune and coagulation systems. Advances in omics technologies hold great potential to cross the hurdles of data insufficiency and data uncertainty that current NP methods encounter. In particular, the transcriptomics data of mRNA expression contains high complexity that allows a sufficient description of perturbations, including single compounds, mixtures of TCMs, or medicated serum. Connectivity Map (CMap), which was first reported in 2006 [13] and updated in 2017 as a next-generation CMap, namely the L1000 platform, with over 1.3 million L1000 profiles [14], presents a systematic approach to investigating the complex connections underlying small molecules and diseases through transcriptomics data. This CMap strategy provides invaluable insights into drug discovery and disease treatment, and it also serves as an enlightening concept for TCMs. To comprehensively describe the molecular mechanism of TCMs, requires the understanding of perturbations, which are the modulated expression of genes and corresponding downstream consequences that TCMs induced in biological systems, as well as alterations of transcriptomic profiles of diseases. At present, the transcriptomic profiles of SARS-CoV-2 infection of primary human lung epithelium for COVID-19 modeling and drug discovery are provided in Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/sars-cov-2/). Whats more, the HERB [15], as a systematic database, has organized the available pharmacotranscriptomics data of 36 herbs. Though it indicated that the research on TCMs has increasingly turned to high-throughput transcriptomic screens for the molecular effects of herbs, perturbations of TCMs against COVID-19 are still lacking. Therefore, one of the opportunities lies in obtaining their transcriptomic profiles. Moreover, the potential implications of

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gene expressions must be integrated with computational strategies (mainly machine learning-based approaches) into network frameworks to generate insights into active compounds, corresponding targets, and diseases.

Despite the aforementioned aspects that are a cause for optimism, some difficulties must also be confronted. Concerning the unexpected and dramatic increase in COVID-19, population-based clinical data regarding dysregulated immune systems or hypercoagulable states must be obtained to allow the investigation of the molecular mechanism of actions of TCMs and permit the evaluation of their effectiveness. Herein such data is awaiting accumulation. Nevertheless, preclinical explorations on cell or animal models would be the first step and eventually contribute to pointing out the direction of collecting and analyzing the clinical data.

Previous studies have indicated the feasibility of NP analysis of TCMs for COVID-19 treatment. Pharmacological research on the mechanisms by which viruses infect their hosts can help us to better understand the potential targets of TCMs [16]. Transcriptomics data-based investigation might allow a more comprehensive NP analysis of TCMs. The identification of differentially expressed genes is simply the first step in this endeavor. Further large-scale investigations on the genetic perturbations of TCMs that utilize novel network models, algorithms, and computational methods are warranted. COVID-19 forces us to urgently face these challenges in NP-based drug discovery. Nevertheless, the opportunities that this undertaking presents must be seized to make TCMs thrive.

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## ADDITIONAL INFORMATION
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