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Editorial

Identification of Bioactive Components in QingFeiPaiDu Decoction for Treatment of COVID-19 by Network Pharmacology

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The outbreak of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has become a major threat to public health around the world. Although different types of vaccines have been developed at an unprecedented pace to prevent the virus from spreading, therapeutics against COVID-19 are still urgently needed for treating infected patients. Otherwise, the morbidity rate of the pandemic is expected to increase. The European Medicines Agency and US Food and Drug Administration (FDA) have approved the treatment of hospitalised COVID-19 patients with remdesivir, a broad-spectrum anti-viral agent that can block the replication of SARS-CoV-2 by inhibiting RNA polymerase of the virus. Remdesivir has been shown to protect hospitalised patients against mortality, but its effects on reducing the needs for mechanical ventilation and shorting hospital stay are uncertain.[1] There are also concerns about the use of remdesivir in severely-ill patients because of the reported adverse effects, including respiratory failure and abnormalities in electrocardiogram.[2,3] Tocilizumab, a monoclonal antibody targeting interleukin-6 receptor, could significantly reduce the respiratory support requirements and inflammatory markers of patients with COVID-19 when administered at the early inflammatory stage (i.e., 8 to 15 days post-symptom onset) in severely-ill patients.[4] Therefore, new drugs for COVID-19 treatment are currently being researched and developed. In a 204-patient phase 2a trial, an oral anti-viral agent called molnupiravir showed to be effective at reducing the nasopharyngeal SARS-CoV-2 infectious virus and viral RNA.[5] On October 1, 2021, Merck announced an interim analysis of a phase 3 study indicating that molnupiravir could reduce the risk of hospitalisation or death by about 50% in patients with mild or moderate COVID-19. At the time of the preparation of this commentary, Pfizer's oral anti-viral agent called PF-07321332 is being tested in clinics.

In addition to these anti-viral agents, treatment of COVID-19 with Traditional Chinese Medicine (TCM) has also been studied. Recently, QinFei PaiDu decoction has been prescribed to 701 patients with COVID-19, resulting in an effective cure rate of over 90% (i.e., 130 cases of complete response and discharge from hospital, 51 cases of disappearance of clinical symptoms, 268 cases of amelioration in symptoms, and 212 cases of stable symptoms without aggravation).[6] Therefore, it is of great interest to identify from the decoction the pharmacological active compounds that could be developed into therapeutics against COVID-19. However, the conventional approach for the discovery of compounds with therapeutic potentials from TCM requires complicated extraction and isolation, followed by characterization using different *in vitro* and *in vivo* assays. The conventional "one-drug-one-target" approach has allowed identifications of hundreds of thousand drug leads, but overlooks the fact that a single therapeutic agent can modulate multiple proteins instead of single targets. A systemic high-throughput strategy that can elucidate the network of proteins and the associated phenotypic changes modulated by a single drug would accelerate new drug discovery.

Over the last two decades, advances in omics technologies (i.e., transcriptome, proteome, metabolome, single nucleotide polymorphism, etc.) and significant increases in computational power have led to the emergence of network biology and polypharmacology. Specifically, network biology is a new paradigm allowing the understanding of the complex interactions between cellular molecules using an integrative and systems approach. Polypharmacology refers to a single drug that acts on multiple targets and is associated with a single or several different signalling pathways. Hopkins AL[7,8] published a network pharmacology approach combining network biology and polypharmacology to discover druggable targets and prediction of the drug-likeness (i.e., optimal efficacy and safety profiles) of newly designed or discovered compounds.

Based on the clinical symptoms of patients with COVID-19, Liu Y *et al*.[9] employed a network pharmacology approach to construct a component-target-disease network that identified bioactive compounds from QingFei PaiDu decoction (QFPDD) for the treatment of COVID-19. QFPDD, which consists of 21 TCMs, is now being used in China for managing patients with COVID-19. The decoction demonstrate the ability to ameliorate COVID-19 symptoms in newly diagnosed patients and to reduce the mortality rate of the severely-ill patients with COVID-19 in hospitals.[10] Through network pharmacology, a total of 376 bioactive components have been identified from the TCMs of QFPDD. Notably, two of them were predicted to demonstrate high-affinity interaction with angiotensinconverting enzyme 2 (ACE2), and 3-chymotrypsinlike

Abbreviations: COVID-19, coronavirus disease 2019; QFPDD, QingFeiPaiDu decoction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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cysteine protease (3CLpro) of SARS-Cov-2. 3CLpro controls viral replication and is considered a promising target for rational-based anti-viral agents. Indeed, there are a few 3CLpro binders being developed as new drugs for COVID-19 treatment.[11] Cellular signalling networks modulated by QPFDD active components have also been deciphered, although validation is still needed through different experiments. For instance, molecular docking experiments can be performed to further validate the network pharmacology results. In addition, the binding of two compounds to 3CLpro and ACE2 requires further biophysical characterisation.

The study by Liu Y provides insights into the molecular mechanisms by which QFPDD could ameliorate COVID-19 symptoms in clinical patients, opening an avenue for developing COVID-19 therapeutics from QFPDD bioactive components. Perhaps more importantly, the study suggests that effective treatment of a complex disease would only be achieved by intervening multiple cellular components with multi-target therapies. The most known multi-target therapy is a combination therapy involving more than one therapeutics. Indeed, the FDA has issued an emergency use authorization for the combined use of remdesivir with baricitinib to treat hospitalised patients (aged > 2 years) with suspected or laboratory confirmed COVID-19 requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.

Moreover, baricitinib is a Janus kinase inhibitor with pronounced anti-inflammatory property. It has been reported that the use of such JAK inhibitors in combination with remdesivir could inhibit viral replication and reduce cytokine storm, leading to beneficial clinical outcomes in patients with COVID-19, especially severely-ill elderly patients.[12] As the number of curated databases of omics and clinical information increases, analysis of these databases using machine/deep learning is critical to further accelerate drug discovery from natural products and compound libraries.

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Conflict of interest

Dr. Kwong Fai Wong has been an editorial board member of *Journal of Exploratory Research in Pharmacology* since June 2021. The author has no other conflicts of interest related to this publication.

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