Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

The pros and cons of traditional Chinese medicines in the treatment of COVID-19

Several traditional Chinese medicines have been recommended by the National Health Commission of China (NHCC) [1] for the treatment of COVID-19. Their clinical beneficiary [2] and adverse [3] effects to the COVID-19 patients have been discussed based on the direct and related clinical evidences. An important question is whether the pros of these traditional medicines outweigh the cons or vice versa for the COVID-19 patients, which is to be clinically resolved. Inflammation regulation is a key mechanism of these traditional medicines against COVID-19 [4]. The discussed adverse effects are largely related to inflammation [3]. Therefore, some indications may be learned from the clinical profiles of the inflammation-associated diseases that involve similar sets of regulators as COVID-19 and have been treated by the same traditional medicines.

The NHCC-recommended traditional medicines have been clinically used or studied for several inflammation-related disease conditions other than viral infections, with the inflammation processes regulated by similar sets of regulators as COVID-19 (Supplementary Table S1). Examples are bacterial infections, diarrhea, chronic obstructive pulmonary disease, pulmonary injury, cancers, and diabetes. *In-vitro* and *in-vivo* studies have led to useful clues to certain common inflammation-regulatory mechanisms of these traditional medicines against COVID-19 [4], viral infections [5] and other inflammation-related disease conditions (Supplementary Table S1). These preclinical clues combined with clinical data analysis are useful for assessing the clinical effects of the traditional medicines against these diseases, particularly with the aid of multi-omics analysis [6]. The assessment results provide useful indications on the pros and cons of these traditional medicines for the COVID-19 patients.

Starting from the chemical ingredients of these traditional medicines (TCM-ID database http://bidd2.nus.edu.sg/TCMID/), we extracted the potent targets (targets of the chemical ingredients with activities $\leq 1\mu M$) (Supplementary Table S2) from the chemogenomics databases (ChEMBL and NPASS), the targeted mechanisms (Table 1 and Supplementary Table S3) from the functional genomics databases (Gene Ontology resource and PubMed), and the clinical gene expression profiles of these targets from the transcriptomics databases (ARCHS4). The differential gene expression profiles of these targets in the lung and blood samples of the patients of the inflammation-related diseases over the healthy individuals were derived using established methods (Supplementary methods, Supplementary Figure S1-S9).

The multi-omics data analysis revealed 17 potent targets of the 8 NHCC-recommended traditional medicines that are overexpressed in > 5% patients of the inflammation-associated disease conditions, the majority (71%) of which are inflammation regulators (Supplementary Table S3). The regulatory roles of these targets (Supplementary Table S4) are consistent with the differentially-recommended clinical utilities of these traditional medicine (Table 1). These traditional medicines universally reduce innate immunity induced inflammation and tissue damage, by targeting specific regulators, including several key regulators that are critical or required for the inflammation processes (Table 1). In particular, a key regulator ALOX15 and a non-key regulator CDK6 is the target of 5 and 6 of the 8 traditional medicines respectively. Significantly, all three medicines for the clinical treatment period target two key regulators, while three of the four medicines for the fever cases of the medical observation period target one key regulator, and the medicine for the non-fever cases target non-key regulators only.

Despite the incomplete investigations, the multi-omics data analysis revealed the inflammation-promoting adverse effects by 5 of the 8 traditional medicines (Table 1), consistent with the reported pneumonitis and lung injury in the patients of interstitial lung diseases given various kampo formulations [3]. These adverse effects mostly arise from the dual pro- and anti-inflammatory effects of the specific regulators targeted by these traditional medicines (Table 1). For instance, some medicines contain both AR inhibitory and activating chemical ingredients, resulting on dual anti- and pro-inflammatory effects. In another case, the targeting of a regulator HTR7 reduces both DC cell mediated inflammation and macrophage-mediated anti-inflammatory activity.

The multi-omics data analysis also provides useful indications about whether the pros of these traditional medicines outweigh the cons for the patients of the inflammation-related disease conditions. For each of the 5 medicines of dual pro and con activities, the largest percentage of the patients with the pro effects vs. those with the con effects are 17% vs. 17%, 32% vs. 7%, 16% vs. 11%, 18% vs. 7%, and 20% vs. 12% (Table 1). Extrapolating these patient profiles into COVID-19, it is indicated that in most cases the pros of these medicines may substantially outweigh the cons for the COVID-19 patients. The beneficiary effects may be more than what were accounted here, considering the additional therapeutic activities of the traditional medicines against COVID-19 [4]. There is a need for further investigations into the pros and cons of the traditional medicines to the COVID-19 patients, and for more attention to the study and monitoring of the potential adverse effects [3].

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Declaration of Competing Interest

There are no conflicts to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104873.

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Table 1
Patent herbal medicines against COVID-19 recommended by the Chinese health organizations, and the mechanisms indicated by the bench-to-clinical multi-OMICS data in the lung and blood samples of the relevant patients. The targets overexpressed in > 5% of the patients are included. The bold targets are critical factors for the relevant effects. The critical factor was judged by the literature report of being critical or required for the effect. Detailed descriptions, key regulators and references 12–26 are in Supplementary Table 3 and 4 respectively.

Clinical Cases Medical observation period	Traditional medicine	Mechanisms Indicated by the Integrative Bench-to-Clinic Muti-omics Data in the Lung and Blood Samples of Patients
Fatigue with gastro-intestinal discomfort	Huoxiang Zhengqi capsules 藿香正气胶囊	Pros: Inhibited CHMR4 and CDK6 in 17% and 15% patients to reduce DC and T cell mediated inflammation [12, 13] and neutrophil-induced tissue damage [14]. Cons: Inhibited CHMR4, PDGES, and MAOA in 17%, 7% and 6% patients to reduce adaptive immune activation [15], and hinder inflammation resolution [16, 17]. Mixed: Inhibited PDGES in 7% patients to hinder dual pro- and anti- inflammatory responses of DC cells [18].
Fatigue with fever	Lianhua Qingwen capsules 连花清瘟胶囊	Pros: Inhibited ALOX15, HTR7 and CDK6 in 32%, 7% and 14% patients to reduce macrophage and DC cell mediated inflammation [19, 20], neutrophil-induced tissue damage [14], and restore DC cell activation of adaptive immunity [15]. Cons: Inhibited HT7R in 7% patients to reduce macrophage-mediated anti-inflammatory activity [21] and restore DC cell mediated inflammation [15].
	Jinhuaqinggan granula 金花清感颗粒	Pros: Inhibited ALOX15 and CDK6 in 19% and 12% patients to reduce macrophage-mediated inflammation [19], and neutrophil-induced tissue damage [14].
	Shufengjiedu capsules 疏风解毒胶囊	Pros: Inhibited CDK6 and IDO1 in 13% and 5% patients to reduce neutrophil-induced tissue damage [14] and restore T helper/effector cell activation [22].
	Fangfengtongsheng pill 防风通圣丸	Pros: Inhibited ALOX15, HTR7, CDK6 and KIT in 16%, 6%, 9% and 11% patients to reduce macrophage and DC cell mediated inflammation [19, 20], neutrophil-induced tissue damage [14], and restore DC cell activation of adaptive immunity [15]. Cons: Inhibited HT7R and KIT in 6% and 11% patients to reduce macrophage-mediated anti-inflammatory activity [21] and restore DC cell mediated inflammation [15, 23].
Clinical treatment period		
Mild, general and severe cases	Qingfeipaidu decoction 清肺排毒汤	Pros: Inhibited ALOX15, MIF and CDK6 in 28%, 5% and 12% patients to reduce macrophage-mediated inflammation [19, 24], and neutrophil-induced tissue damage [14].
Critical cases	Suhexiang pill 苏合香丸	Pros: Inhibited MIF and AR in 18% and 7% patients to reduce macrophage and neutrophil mediated inflammation [24, 25], and restore T-cell/B-cell development in adaptive immunity [25], activated GPER1 in 6% patients to reduce monocyte-mediated immune response and inflammation [26]. Cons: Activated AR in 7% patients to promote neutrophil mediated inflammation [25].
	Angongniuhuang pill 安宫牛黄丸	Pros: Inhibited ALOX15, AR and KIT in 20%, 8% and 12% patients to reduce macrophage and neutrophil mediated inflammation [19, 25], restore DC cell activation [19] and T-cell/B-cell development [25] of adaptive immunity, activated GPER1 in 6% patients to reduce monocyte-mediated immune response and inflammation [26]. Cons: Inhibited KIT in 12% patients to restore DC cell mediated inflammation [23]. Activated AR in 8% patients to promote neutrophil mediated inflammation [25].

References

[1] Y.H. Jin, L. Cai, Z.S. Cheng, H. Cheng, T. Deng, Y.P. Fan, C. Fang, D. Huang, L.Q. Huang, L.Q. Huang, Y. Han, B. Hu, F. Hu, B.H. Li, Y.R. Li, K. Liang, L.K. Lin, L.S. Luo, J. Ma, L.L. Ma, Z.Y. Peng, Y.B. Pan, Z.Y. Pan, X.Q. Ren, H.M. Sun, Y. Wang, Y. Wang, H. Weng, C.J. Wei, D.F. Wu, J. Xia, Y. Xiong, H.B. Xu, X.M. Yao, Y.F. Yuan, T.S. Ye, X.C. Zhang, Y.W. Zhang, Y.W.G. Zhang, H.M. Zhang, Y. Zhao, M.J. Zhao, H. Zi, X.T. Zeng, Y. Wang, X.H. Wang, Management ftZHoWUNC, Research Team E-BMCoCIE, Promotive Association for M, Health C. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version), Mil. Med. Res. 7 (1) (2020) 4.

[2] J.L. Ren, A.H. Zhang, X.J. Wang, Traditional Chinese medicine for COVID-19 treatment, Pharmacol. Res. 155 (2020) 104743.

[3] P.E. Gray, Y. Belessis, The use of Traditional Chinese Medicines to treat SARS-CoV-2 may cause more harm than good, Pharmacol. Res. 156 (2020) 104776.

[4] L. Runfeng, H. Yunlong, H. Jicheng, P. Weiqi, M. Qinhai, S. Yongxia, L. Chufang, Z. Jin, J. Zhenhua, J. Haiming, Z. Kui, H. Shuxiang, D. Jun, L. Xiaobo, H. Xiaotao, W. Lin, Z. Nanshan, Y. Zifeng, Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2), Pharmacol. Res. (2020) 104761.

[5] Y. Ding, L. Zeng, R. Li, Q. Chen, B. Zhou, Q. Chen, P.L. Cheng, W. Yutao, J. Zheng, Z. Yang, F. Zhang, The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function, BMC Complement. Altern. Med. 17 (1) (2017) 130.

[6] K.J. Karczewski, M.P. Snyder, Integrative omics for health and disease, Nat. Rev. Genet. 19 (5) (2018) 299–310.

Yali Wang[a,b], Xian Zeng[c], Yufen Zhao[a], Weiping Chen[d,*], Yu Zong Chen[b,*]

[a] *The Institute of Drug Discovery Technology, Ningbo University, Ningbo 315211, PR China*

[b] *Bioinformatics and Drug Design Group, Department of Pharmacy, National University of Singapore, 117543, Singapore*

[c] *Department of Biological Medicines & Shanghai Engineering Research Center of Immunotherapeutics, Fudan University School of Pharmacy, Shanghai 201203, PR China*

[d] *Key Lab of Agricultural Products Processing and Quality Control of Nanchang City, Jiangxi Agricultural University, Nanchang 330045, PR China*

E-mail addresses: iaochen@163.com (W. Chen), phacyz@nus.edu.sg (Y.Z. Chen).

* Corresponding authors.