Chinese Journal of Integrative Medicine
Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
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Original Article

Chinese Medicine Meets Conventional Medicine in Targeting COVID-19 Pathophysiology, Complications and Comorbidities*

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ABSTRACT **Objective:** To investigate how the National Health Commission of China (NHCC)-recommended Chinese medicines (CMs) modulate the major maladjustments of coronavirus disease 2019 (COVID-19), particularly the clinically observed complications and comorbidities. **Methods:** By focusing on the potent targets in common with the conventional medicines, we investigated the mechanisms of 11 NHCC-recommended CMs in the modulation of the major COVID-19 pathophysiology (hyperinflammations, viral replication), complications (pain, headache) and comorbidities (hypertension, obesity, diabetes). The constituent herbs of these CMs and their chemical ingredients were from the Traditional Chinese Medicine Information Database. The experimentally-determined targets and the activity values of the chemical ingredients of these CMs were from the Natural Product Activity and Species Source Database. The approved and clinical trial drugs against these targets were searched from the Therapeutic Target Database and DrugBank Database. Pathways of the targets was obtained from Kyoto Encyclopedia of Genes and Genomes and additional literature search. **Results:** Overall, 9 CMs modulated 6 targets discovered by the COVID-19 target discovery studies, 8 and 11 CMs modulated 8 and 6 targets of the approved or clinical trial drugs for the treatment of the major COVID-19 complications and comorbidities, respectively. **Conclusion:** The coordinated actions of each NHCC-recommended CM against a few targets of the major COVID-19 pathophysiology, complications and comorbidities, partly have common mechanisms with the conventional medicines.

KEYWORDS COVID-19, Chinese medicine, target, therapeutic mechanism, pathophysiology, comorbidity

Several Chinese medicines (CMs) have been recommended by the National Health Commission of China (NHCC) for the treatment of coronavirus disease 2019 (COVID-19).[1,2] Also, these CMs have been recommended for different clinical phenotypes. Significant clinical efficacy and safety of NHCC-recommended CMs have recently been reported based on a multicenter, prospective and randomized controlled trial[3] and a retrospective analysis[4] of the CM-treated COVID-19 patients. Nonetheless, concerns have been raised about the lack of understanding of the therapeutic mechanisms and the insufficient attention to the clinical adverse effects of these CMs.[5-7] As part of the efforts for resolving these concerns, investigations have been conducted for probing the mechanisms, particularly the targets and regulated networks, of the CMs for the treatment of COVID-19.[8-14] These investigations have revealed the possible targets of the NHCC-recommended CMs in the modulation of the COVID-19 pathological processes, particularly the inhibition of COVID-19 replications,[8,10] the modulation of hyperinflammations,[9,10,15] and the reduction of tissue

*Supported by the National Natural Science Foundation of China (No. 21778042) and Singapore Academic Funds (No. R-148-000-273-114)

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DOI: https://doi.org/10.1007/s11655-022-3573-0

damages.[15] The clinical relevance of these targets may be interrogated by 2 target-evaluation rules.[12,15] Firstly, these targets must be potently (i.e. activity cut-off value ⩽1 μmol/L) modulated by the CM based on solid experimental evidence (henceforth named potent targets). Secondly, these potent targets must be clinically validated, either with an existing approved or clinical trial drug modulating the same target, or with significantly upregulated gene expression in substantial patient populations for indicating the active involvement in the disease processes.

By using these target-evaluation rules, we have in our earlier works conducted 2 investigations of the NHCC-recommended CMs.[12,15] It has revealed 24 experimentally-determined potent targets of 8 NHCC-recommended CMs upregulated in >5% of the patients of inflammation-related diseases, 71% of them are hyperinflammation regulators.[15] Significantly, each individual CM modulates a few hyperinflammation regulators with dual inflammation inhibitory (pro) and promoting (con) effects,[15] consistent with the reported clinical beneficiary[3,4] and adverse effects[6] in the COVID-19 patients. The estimated percentages of the COVID-19 patients of the pro and con effects in Lianhua Qingwen Capsules (连花清瘟胶囊) are 16%–32% and 7%–17%, respectively, with up to 25% more pro effect patients than con effect patients,[15] which is consistent with the 19.8% and 12.7% higher clinical improvement and cure rates of the Lianhua Qingwen Capsules treatment group over the control group in the COVID-19 clinical trial.[3] In the second investigation,[12] we have compared the experimentally-determined potent targets of 8 NHCC-recommended CMs with the targets discovered by the 2 recent COVID-19 target discovery studies.[16,17] Significantly, 4 potent targets of 6 CMs have been discovered as the targets against COVID-19 pathophysiology. In particular, 3 of the 4 targets are with clinical trial drugs and thus of high drug repurposing potential, and 2 of these 3 targets modulate macrophage-mediated hyperinflammations. Our study suggests that the East (CM) meets West (conventional medicine) in common therapeutic mechanisms against COVID-19 pathophysiology,[12] and these common targets are thus clinically-validated CM targets against COVID-19.

Given the success of these target-evaluation rules for finding the clinically-relevant targets of CMs against COVID-19 pathophysiology,[12,15] one may question whether these rules can be explored for further investigating the multiple mechanisms of CMs against COVID-19. CMs are formulated for the coordinated modulation of multiple pathological factors and maladjustments that lead to complications and comorbidities of the patients.[18-20] The major COVID-19 complications include fever, cough, pain, anorexia and headache in 45%–61%, 34%–50%, 14%–77%, 24%–32%, and 13%–17% of the COVID-19 patients, respectively.[21,22] The major COVID-19 comorbidities include hypertension, obesity, and diabetes in 30%–57%, 12%–42% and 15%–34% of the COVID-19 patients, respectively, which are linked to the disease severity[23-26] and higher death rates.[27] Therapeutic targeting of these COVID-19 complications and comorbidities significantly impact the disease progression. It is of interest to investigate which and how the major COVID-19 complications and comorbidities are modulated by the NHCC-recommended CMs, particularly by common mechanisms with the conventional medicines. We therefore applied target-evaluation rules[12,15] to analyze the experimentally-determined potent targets of 11 NHCC-recommended CMs (Appendix 1) for searching the common targets with respect to the 3 sets of targets of conventional medicines. The first set contains the targets of COVID-19 pathophysiology discovered by the COVID-19 target discovery studies.[16,17] The second and third sets are the targets of the approved or clinical trial drugs for the treatment of the major COVID-19 complications and comorbidities, respectively. The common targets were selected based on the match in both target protein and activity type (inhibition/antagonism or activation/agonism).

METHODS

CMs and Target Data Collection

NHCC-recommended CMs for the treatment of COVID-19 were collected from the 5th and 7th editions of the NHCC guidelines.[1] The constituent herbs of these CMs and their chemical ingredients were from the Traditional Chinese Medicine Information Database (TCM-ID).[28] The experimentally-determined targets and the activity values of the chemical ingredients of these CMs were from the Natural Product Activity and Species Source Database (NPASS).[29] An activity [half maximal inhibitory concentration (IC_{50}) or inhibition constant (Ki)] cut-off value of ⩽1 μmol/L was used for selecting the potent targets of these CMs. The reference record

(PMID or DOI) for each ingredient-target activity value was from the NPASS database,[29] and the activity type (inhibition/antagonism or activation/agonism) were from the corresponding literatures.

Drugs and Target Data Collection

The targets discovered by the 2 COVID-19 target discovery studies and the corresponding approved and clinical trial drugs were from the relevant publications.[16,17] Additional approved and clinical trial drugs against these targets were searched from the Therapeutic Target Database (TTD)[30] and DrugBank Database.[31] The approved and clinical trial drugs against the major COVID-19 complications and comorbidities and the targets of these drugs were searched from the TTD and DrugBank databases by using the names of the complications and comorbidities. The pathways of the targets are from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database[32] and additional literature search. Literature was searched for removing the same drug of alternative names and confirming they are clinically used against the respective complications and comorbidities.

CM Target Analysis

The clinically-relevant targets of CMs are modulated by the constituent herbs to produce distinguished potent activities. These herbs belong to certain traditionally-characterized classes. The larger classes are heat clearing and detoxification (50 herbs), qi regulating (41 herbs), cough and asthma (29 herbs), heat clearing and fire purging (23 herbs), divergent wind chill (21 herbs), and divergent wind fever (20 herbs). The clinical effects of each class likely arise from potent activities against more than 1 target distinguished from the targets of other classes. Therefore, the clinically-relevant targets of CMs are expected to be non-ubiquitous targets, i.e., they are the potent targets of limited number of herbs. Based on the numbers of herbs in the larger classes, we tentatively set a non-ubiquitous target threshold of no more than 30 herbs. Variation of the cut-off values from 25 and 35 herbs only led to small variations of the results. The non-ubiquitous potent targets of CMs were compared to the targets of the 2 COVID-19 target discovery studies,[16,17] and the targets of the approved or clinical trial drugs for the treatment of the major COVID-19 complications and comobidities. For the matched targets, the activity type of each CM ingredient and drug were further compared, and the targets of matched activity types were recorded as the targets of the common targets of CMs and drugs. The network graphs of the identified common targets were constructed by using Cytoscape (version 3.7.2, supported by the U.S. National Institute of General Medical Sciences).[33]

RESULTS

Targets of NHCC-Recommended CMs for Treatment of COVID-19

Of the 11 NHCC-recommended CMs (Appendix 1), 5 CMs are for the medical observation period before diagnosis, and 6 CMs for the clinical treatment period. In particular, 3 established CMs [Lianhua Qingwen Capsules, Jinhua Qinggan Granules (金花清感颗粒), and Xuebijing Injection (血必净注射液)] and 3 recipes [Qingfei Paidu Decoction (清肺排毒汤), Xuanfei Baidu Formula (宣肺败毒方), and Huashi Baidu Formula (化湿败毒方)] have shown clinical efficacies in COVID-19 patients.[3,34] Appendix 2 lists the constituent herbs, chemical ingredients, the experimentally-determined potent targets and activity values of these 11 CMs. Appendix 3 provides the comparison of the potent targets and activity types of the CMs with the 3 sets of targets of conventional medicines. Several common targets were identified. The graphic view of these targets and the matched CMs and drugs are shown in Figure 1.

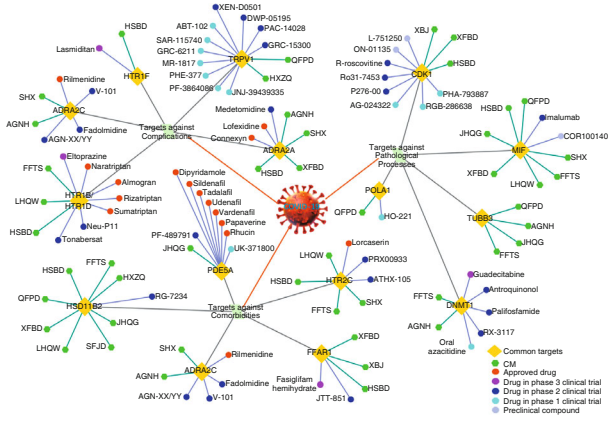

Figure 1. Graphic View for Common Targets of NHCC-Recommended CMs with Respect to 3 Sets of Targets of Conventional Medicines

Notes: The targets of conventional medicines include the targets of the recent target discovery studies against COVID-19 pathological processes, and the targets of the approved or clinical trial drugs for the treatment of COVID-19 complications and comorbidities, respectively. Only the drugs that match the activity type of the corresponding CMs are shown, the same below. HXZQ: Huoxiang Zhengqi Capsules; LHQW: Lianhua Qingwen Capsules; JHQG: Jinhua Qinggan Granules; SFJD: Shufeng Jiedu Capsules; FFTS: Fangfeng Tongsheng Pills; XFBD: Xuanfei Baidu Formula; QFPD: Qingfei Paidu Decoction; HSBD: Huashi Baidu Formula; XBJ: Xuebijing Injection; SHX: Suhexiang Pills; AGNH: Angong Niuhuang Pills; the same below

Common Targets of CMs and Conventional Drugs against COVID-19 Pathophysiology

The viral pathological processes are promoted by the virus-host protein interactions and virus-induced host protein upregulations, which have been the focuses of the COVID-19 target discovery studies.[16,17] We identified 5 common targets of 9 NHCC-recommended CMs with respect to the targets revealed by these target discovery studies,[16,17] each CM modulating at least 1 inflammation regulatory target (Appendix 4). These 5 common targets are all inhibited by the matched CMs and drugs, and 4 of them are the targets of approved or clinical trial drugs with drug repurposing potential. As shown in Figure 2, 1 identified target MIF is a common target of 7 CMs [Fangfeng Tongsheng Pills (防风通圣丸), Suhexiang Pills (苏合香丸), Qingfei Paidu Decoction, Jinhua Qinggan Granules, Lianhua Qingwen Capsules, Xuanfei Baidu Formula, and Huashi Baidu Formula]. This target is in the top-3 ranked protein clusters of the targets revealed by the proteomics-based COVID-19 target discovery study.[17] MIF is a critical mediator of macrophage inflammatory cytokine production and innate immune responses,[35] and is targeted by a phase 2 (imalumab) and a preclinical (COR100140) inhibitor drug against cancers and inflammation, respectively.

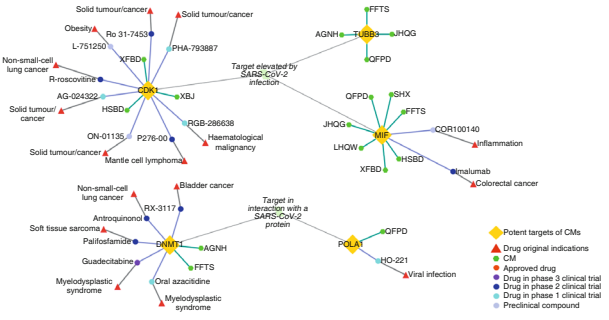

Figure 2. Common Targets of NHCC-Recommended CMs with Respect to Two Recent COVID-19 Target Discovery Studies

Another identified target DNMT1 is a common target of 2 CMs [Fangfeng Tongsheng Pills and Angong Niuhuang Pills (安宫牛黄丸)], which interacts with COVID-19 ORF8 protein.[16] DNMT1 regulates macrophage inflammation[36] and T-cell development,[37] and is targeted by 5 inhibitor drugs in cancer clinical trials (guadecitabine, antroquinonol, palifosfamide, RX-3117, and oral azacitidine). The third common target CDK1 of 3 CMs (Xuanfei Baidu Formula, Huashi Baidu Formula, and Xuebijing Injection) has been discovered by the proteomics-based COVID-19 target discovery study.[17] It reportedly regulates replications of certain viruses,[38] and is targeted by 6 inhibitor drugs in clinical trials (Ro 31-7453, AG-024322, PHA-793887, P276-00, R-roscovitine, RGB-286638) and 2 preclinical drugs (ON-01135, L-751250) against cancers and obesity.

The fourth target POLA1 of 1 CM (Qingfei Paidu Decoction) has been discovered by the interactomics-based COVID-19 target discovery study.[16] It is a critical regulator of type Ⅰ interferon inflammatory response,[39] and is targeted by an inhibitor drug (HO-221) in clinical trial against viral infections. The fifth target TUBB3 of 4 CMs (Fangfeng Tongsheng Pills, Angong Niuhuang Pills, Qingfei Paidu Decoction, and Jinhua Qinggan Granules) has also been discovered by the interactomics-based COVID-19 target discovery study.[16] TUBB3 is a tubulin that interacts with viral protein to facilitate viral transcription.[40,41] These common targets indicate the common mechanisms of CMs and conventional medcines in targeting macrophage-mediated inflammation andviral replication processes in COVID-19.

Interestingly, 7 of the 9 identified NHCC-recommended CMs for the treatment of particular phenotypes appear to target distinguished sets of common targets that are different from the CMs for the other phenotypes. As shown in Appendixes 1 and 4, there are 3 CMs (Lianhua Qingwen Capsules, Jinhua Qinggan Granules, and Fangfeng Tongsheng Pills) for the treatment of the phenotype of fatigue with fever in the medical observation period, which either target MIF or co-target MIF and TUBB3 or simultaneouslly target MIF, TUBB3 and DNMT1. There is 1 CM (Xuanfei Baidu Formula) for the treatment of 2 phenotypes of mild and general cases in the clinical treatment period, which targets CDK1 and MIF. There are 3 CMs (Huashi Baidu Formula, Qingfei Paidu Decoction, and Xuebijing Injection) for the treatment of the phenotype of severe cases in the clinical treatment period (Xuebijing Injection is also for critical cases), the first two of which either co-target POLA1 and MIF or simultaneously target POLA1, MIF, and TUBB3. There are 3 CMs (Angong Niuhuang Pills, Suhexiang Pills, and Xuebijing Injection) for the treatment of the phenotype of critical cases in the clinical treatment period (Xuebijing Injection is also for severe cases), the first one of which targets DNMT1 and TUBB3. Nonetheless, there are 2 CMs with unclear phenotype-

target association. Specifically, Suhexiang Pills for the critical cases and Xuebijing Injection for the critical and severe cases in the clinical treatment period are each with 1 common target (CDK1 and MIF) only, which are not distinguished from the targets of the CMs for the other phenotypes. One possible reason is that not all targets of these 2 CMs have been revealed by the COVID-19 target discovery studies[16,17] because of limited patient populations in the investigations.

Common Modulated Proteins of CMs and Conventional Drugs Against Major COVID-19 Complications

For the 5 major COVID-19 complications,[21,22] we identified 6 potent modulated proteins of 8 NHCC-recommended CMs in common with the targets of drugs against 2 major COVID-19 complications pain and headache (Appendix 5). Specifically, 1 CM modulates a target of pain and a target of headache, 5 CMs modulate a target of pain, and 2 CMs modulate a target of headache (Figure 3). ADRA2A is agonized by 4 CMs (Suhexiang Pills, Angong Niuhuang Pills, Xuanfei Baidu Formula, and Huashi Baidu Formula) and a phase 2 drug against pain (medetomidine). ADRA2C is agonized by 2 CMs (Suhexiang Pills and Angong Niuhuang Pills) and a phase 2 drug (fadolmidine) against pain. ADRA2 subtypes regulate neuroactive ligand-receptor interaction and cyclic guanosine monophosphate-protein kinase G (cGMP-PKG) signaling. Their agonists produce analgesia, anxiolysis, sedation, and sympatholysis effects for the treatment of chronic pains.[42] TRPV1 is inhibited by 2 CMs [Huoxiang Zhengqi Capsules (藿香正气胶囊) and Qingfei Paidu Decoction] and 8 clinical trial drugs against pain (DWP-05195, GRC-15300, MR-1817, PF-3864086, PHE-377, SAR-115740, ABT-102, and JNJ-39439335). TRPV1 is a multimodal sensor of noxious stimuli that triggers counteractive measures against pain and injury, and TRPV1 activation leads to chronic inflammatory pain and peripheral neuropathy, making TRPV1 a promising target against pain.[43]

There are 3 common modulated proteins against headache. Two proteins are 5-hydroxytryptamine (5-HT) receptor subtypes HTR1B/ HTR1D agonized by 3 CMs (Fangfeng Tongsheng Pills, Lianhua Qingwen Capsules, and Huashi Baidu Formula) and 4 agonist drugs (naratriptan, almogran, rizatriptan, and sumatriptan) against migraine. Another protein HTR1F is agonized by 1 CM (Huashi Baidu Formula) and 1 agonist drug

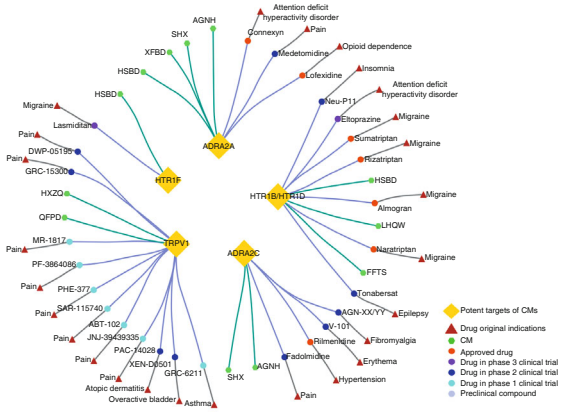

Figure 3. Graphic View of Common Modulated Proteins of NHCC-Recommended CMs and Conventional Drugs against Major COVID-19 Complications

(lasmiditan) in clinical trial against migraine. The 5-HT receptor subtypes HTR1B/ HTR1D and HTR1F mediate neuroactive ligand-receptor interactions and subsequently with migraine pathophysiology.[44] The agonists of these receptor subtypes have been developed as subtype-selective drugs against migraine.[45]

Common Modulated Proteins of CMs and Conventional Drugs against Major COVID-19 Comorbidities

Of the 3 major COVID-19 comorbidities reported in the literatures,[23-26] we identified 5 potent modulated proteins of 11 NHCC-recommended CMs in common with the targets of drugs against 3 major COVID-19 comorbidities (hypertension, obesity, and diabetes, Appendix 6). Specifically, 1 CM (Jinhua Qinggan Granules) modulates a hypertension and a diabetes target, 1 CM (Suhexiang Pills) modulates a hypertension and an obesity target, 3 CMs (Fangfeng Tongsheng Pills, Lianhua Qingwen Capsules, and Huashi Baidu Formula) modulate an obesity and a diabetes target, 1 CM (Angong Niuhuang Pills) modulates a hypertension target, and 5 CMs (Xuanfei Baidu Formula, Xuebijing Injection, Huoxiang Zhengqi Capsules, Qingfei Paidu Decoction, and Shufeng Jiedu Capsules) modulate a diabetes target, respectively (Figure 4). ADRA2C is agonized by 2 CMs (Suhexiang Pills and Angong Niuhuang Pills) and 1 agonist drug (rilmenidine) approved for hypertension. ADRA2 receptor agonists have been used for hypertension and patients withdrawing from long-term abuse of drugs or alcohol.[42] At lower doses, these agonistsblock the sympathetic arm of the autonomic nervous system mediated by the α2A-adrenergic receptor subtype, thereby producing the antihypertensive effects.[42]

The second modulated protein PDE5A is inhibited by 1 CM (Jinhua Qinggan Granules) and 1 inhibitor drug (dipyridamole) approved for hypertension. PDE5 subtypes regulate cGMP-PKG signaling in pulmonary vascular homeostasis, and PDE5 inhibitors have been used for pulmonary arterial hypertension.[46]

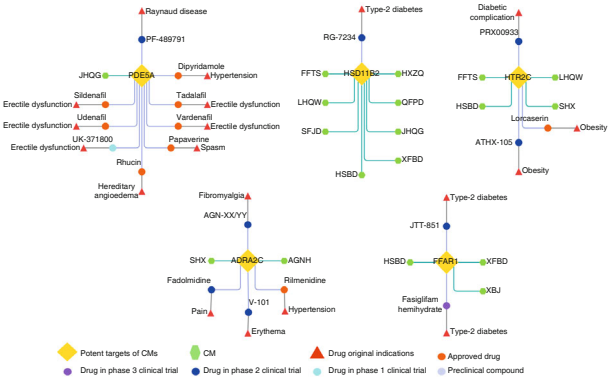

Figure 4. Graphic View of Common Modulated Proteins of NHCC-Recommended CMs and Conventional Drugs against Major COVID-19 Comorbidities

There is 1 common modulated protein against obesity, which is HTR2C agonized by 4 CMs (Fangfeng Tongsheng Pills, Suhexiang Pills, Lianhua Qingwen Capsules, and Huashi Baidu Formula) and 2 agonist drugs (lorcaserin, ATHX-105) approved or in phase 2 trial against obesity. Partly due to the regulation of the brain serotonin (5-HT) system, HTR2C agonists reduce feeding and body weight to elicit anti-obesity effects.[47] There are 2 common modulated proteins against diabetes. One protein FFAR1 is agonized by 3 CMs (Xuanfei Baidu Formula, Huashi Baidu Formula, and Xuebijing Injection) and 2 agonist drugs (Fasiglifam, JTT-851). FFAR subtypes regulate energy metabolism in adipose tissue, and are targeted against metabolic disorders such as diabetes.[48] The second modulated protein HSD11B2 is inhibited by 8 CMs [Huoxiang Zhengqi Capsules, Fangfeng Tongsheng Pills, Qingfei Paidu Decoction, Lianhua Qingwen Capsules, Jinhua Qinggan Granules, Shufeng Jiedu Capsules (疏风解毒胶囊), Xuanfei Baidu Formula, and Huashi Baidu Formula] and 1 inhibitor drug (RG-7234) in clinical trial against diabetes. HSD11B2 regulates diabetes by activating cortisone to cortisol hormone biosynthesis, leading to hypercortisolism associated with metabolic syndromes.[49]

DISCUSSION

The common targets of the NHCC-recommended CMs and the COVID-19 target discovery studies can be divided into 2 groups. The first group contains cytokines and regulators, which include a cytokine (MIF targeted by 7 CMs) for inflammatory responses,[35] a DNA methyltransferase (DNMT1 targeted by 2 CMs) for epigenetic regulation of macrophage-mediated inflammation,[50] and a DNA polymerase (POLA1 targeted by 1 CM) for modulating the activation of certain cytokines.[39] The second group contains viral replication regulators, which include a cell-cycle regulator (CDK1 targeted by 3 CMs) for facilitating viral replications,[38] and a tubulin (TUBB3 targeted by 4 CMs) for promoting the viral genome transcription.[40,41] Experimental studies have confirmed that CMs such as Lianhua Qingwen Capsules repress COVID-19 partly by regulating proinflammatory cytokines and viral replications.[8] Cytokine regulation is a key antiinflammatory mechanism of CM herbs.[51] Our study is consistent with these findings.

The common modulated protein analysis with respect to the conventional medicines is useful for identifying the clinically-relevant targets of CMs. This approach nonetheless has limitations. Firstly, the focus of the common modulated proteins with respect to the proteomics and interact omics studies limits the investigation scope of CM targets. For instance, experimental studies have revealed that Lianhua Qingwen Capsules markedly reduce multiple proinflammatory cytokines [tumor necrosis factor (TNF-α), interleukin-6 (IL-6), C-C motif chemokine 2 (CCL-2/MCP-1) and C-X-C motif chemokine 10 (CXCL-10/IP-10)].[8] *In vivo* and/or *in vitro* studies have revealed that the anti-inflammatory effects of CMs may arise from several mechanisms, including the regulation of transcription factors (e.g. nuclear factor kappa-B), proinflammatory cytokines, intercellular adhesion molecules and proinflammatory mediators such as inducible nitric oxide synthase.[51] Experimental and molecular studies of Xuebijing Injection has found that it has vascular endothelial protection effects as well as anti-inflammatory and immunoregulatory effects partly by cytokine regulations (IL-1, IL-6, IL-8, IL-17 and TNF-α), increase of the Th1/Th2 ratio, improvement of the proportion of Th1 cells, and promotion of the apoptosis of $CD4^+$ $CD25^+$ T cells.[52] Moreover, Xuebijing Injection reportedly regulates coagulation disorders, antagonizes endotoxin, improves immune function and microcirculation.[52] Many of these CM-

regulated processes are manifested in COVID-19,[53,54] but are not yet fully covered by the proteomics and interactomics based target discovery studies.

Secondly, the focus of the common targets neglects network regulatory effects of the CMs. *In silico* and experimental study of Qingfei Paidu Decoction in COVID-19 infected cells has found a network of targets enriched in the regulation of several process, including the interaction, catalysis and activity regulation of proteins in subcellular organelles and cell membrane.[9] A study of Qingfei Paidu Decoction has shown that its major chemical ingredients target distinguished nodes of the target-pathway-disease networks associated with the regulation of antiviral, antiinflammatory activity and metabolic programming.[55] Network pharmacology study of CMs against COVID-19 has also indicated that CMs regulate IL-17 and TNF pathway.[56] The coordinated modulations of CMs against these pathways are inadequately covered by the proteomics and interactomics based studies.

Thirdly, the focus on the potent targets neglects the synergistic actions of CMs. Analysis of the 124 experimentally-determined synergistic combinations of natural products has revealed that it is possible to assemble the sub-potent natural products into highly-potent combinations albet at low probabilities.[57] The CMs for COVID-19 therapeutics[3] likely involve highly-potent synergistic combinations of the chemical ingredients. Indeed, several studies have suggested that the potency-enhancing synergistic effects of the CMs are important parts of the mechanisms against COVID-19[58,59] as well as other diseases.[60,61] These synergistic effects may provide useful clues for the development of the COVID-19 cocktail therapies in conventional medicines. Hence, there is a need for more comprehensive investigations of the synergistic actions in CMs.

In conclusion, NHCC-recommended CMs have exhibited significant clinical effects,[3,4] partly arise from the mechanisms in common with conventional medicines.[12] Our investigation here showed that individual NHCC-recommended CMs not only modulate the COVID-19 pathological processes, but also modulate the major COVID-19 complications and comorbidities, partly in common mechanisms with the conventional medicines. This conforms to the CM formulation principle of co-targeting the pathological factors and maladjustments.[18] Moreover, CMs produce beneficiary effects by synergistic activities[62] against relevant biological networks.[63] In some cases, chemical ingredients of sub-potent activities can be synergistically combined into potent combinations.[57] Therefore, further investigations of various potent and clinically-active targets of CMs from the perspectives of network regulations and synergistic activities may enable deeper understanding of the mechanisms of the NHCC-recommended CMs against COVID-19 pathophysiology, complications and comorbidities.

Conflict of Interest

The authors declare no competing interests.

Author Contributions

Chen YZ conceived and designed this research. Wang SS collected and analyzed the data. Zeng X contributed analytic tools. Wang YL and ZD provided constructive suggestions. Zhao YF reviewd the manuscript. Wang SS and Chen YZ wrote the paper.

Electronic Supplementary Material: Supplementary material (Appendixes 1–6) is available in the online version of this article at https://doi.org/10.1007/s11655-022-3573-0.

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(Accepted May 6, 2021; First Online May 18, 2022)
Edited by YU Ming-zhu