Letter to the Editor

# The database-based strategy may overstate the potential effects of traditional Chinese medicine against COVID-19

The Coronavirus Disease 2019 (COVID-19) pandemic has become a huge threat to global health and developing an efficient therapeutic strategy will be of huge benefit [1]. Traditional Chinese medicine (TCM) plays an indispensable role in the prevention and treatment of several epidemic diseases with a long history. TCM scheme was also included in the Chinese guideline on diagnosis and treatment of COVID-19, and a number of clinical practices demonstrated that TCM exerts positive effects against COVID-19 through increasing the cure rate of western medicine, improving the aggravation and concomitant symptoms of COVID-19 [2,3]. Generally, it is the active ingredients that contribute to the therapeutic effects of TCM on COVID-19, thus the deciphering of comprehensive information of active ingredients is in intense demand [4,5]. Besides literature surveys and chemical methods, the natural product and traditional medicine databases seem to be a popular or efficient tool in the mechanistic investigation of TCM on COVID-19. Recently, Jiang et al. reported that some databases will facilitate mechanistic investigations of TCM against COVID-19 [5], but due to the limitations of database itself, this is open to question.

Many natural product and traditional medicine databases such as TCMSP, TCMID, TCM-ID, SYMMAP, ETCM, NPASS and YATCM are now available as open-source. As shown in Table 1, each of them is flooded with massive information including TCM formulas, herbs, ingredients, targets, diseases, and the details under the corresponding items. Of note, some of them were built by data mining and manually collection from TCM classics, research articles, and E-library, while others were even built by integrating different databases (both SYMMAP and TCMID integrate TCMSP and TCM-ID). So, the quality of collected information and the characteristics of each databases were worth considering. Moreover, the latest update time of TCMSP, TCMID, TM-MC, SYMMAP, CHEM-TCM, NPASS, ETCM, YATCM, and TCM-PTD was 2014, 2016, 2018, 2018, 2011, 2018, 2018, 2018, and 2012, respectively. It is questionable whether overly lagging knowledge can facilitate mechanistic investigations of TCM against COVID-19.

We have retrieved research articles (80 in total) about TCM against COVID-19 which were based on database-based strategy from PubMed and CNKI as of June 15, 2020. The results of database usage frequency were shown in Table 1, in which 73 of 80 articles were used TCMSP for further analysis, the following were ETCM (12 of 80) and TCMID (9 of 80), but none of them were updated earlier than November 2018. It was found that many studies have attempted to determine the anti-COVID-19 activity of ingredients from TCM solely by the binding ability of ingredients with angiotensin-COnverting enzyme 2 (ACE2) through molecular docking, since the increased expression of ACE2 were reported to facilitate infection with COVID-19 [6]. However, most of the active ingredients screened out in these studies are widely present in most Chinese herbs, such as quercetin (PubChem CID: 5280343), kaempferol (PubChem CID: 5280863), luteolin (PubChem CID: 5280445), rutin (PubChem CID: 5280805) and β-sitosterol (PubChem CID: 222284), etc., which seem not the characteristic compound and have yet to validate their anti-COVID-19 activities. Moreover, in these studies, the main focus is on constructing the interaction of herb-ingredient-target protein (Homo sapiens) to predict and analyze the effect of TCM against COVID-19, but it ignores whether these ingredients have a direct antiviral effect on SARS-COronavirus 2 (SARS-COV-2). Subsequently, a total of 56 kinds of Chinese medicines (including Chinese patent medicine, TCM formula/decoction, herb pair, and single herb, etc.) were involved in these articles (Table S1), however, only a few of them (such as Lianhua Qingwen capsules, Qingfeipaidu decoction, Ma Xing Shi Gan decoction, and Shufengjiedu capsules etc.) have been recommended by the National Health Commission of China (NHCC) for the treatment of COVID-19 clinically [1,7]. Importantly, 36 kinds of Chinese medicines have not been validated experimentally or clinically in the treatment of COVID-19, indicating that database-based strategy to repurpose these Chinese medicines for the clinical management of COVID-19 should be more cautious. Compared with Chinese patent medicines, these TCM formulas/decoctions consist of several or even dozens of herbs without corresponding quality criteria, which may pose a challenge to their quality control and database-based mechanistic investigations.

In Chinese clinic, the combination of Chinese and Western medicines is still the mainstream for the treatment of COVID-19, so elucidating the exact role of these TCMs is in urgent demand and the database-based strategy will facilitate the mechanistic investigations of these clinically effective TCMs on COVID-19 to some extent. It is also worth noting that although ACE2 may be an ideal target for preventing COVID-19, we do not yet know whether it is safe to interfere with the normal operation of ACE2. Other receptors/targets of SARS-CoV-2 should also be explored to avoid research gridlock. Furthermore, the quality control and mechanistic investigations of TCM need to be strengthened so that TCM can be acceptable and beneficial for COVID-19 patients worldwide.

Collectively, if the above issues are not solved in time, the abuse of databases will impede mechanistic investigations of TCM against COVID-19, but also may be counterproductive.

**Table 1**
The main characteristics of natural product and traditional medicine databases.

| Database | TCMSP | ETCM | TCMID | SYMMAP | NPASS | CMAUP |
|---|---|---|---|---|---|---|
| Website | http://tcmsp.com/tcmsp.php | http://www.tcmip.cn/ETCM/index.php/Home/Index/ | http://119.3.41.228:8000/tcmid/ | https://www.symmap.org/ | http://bidd2.nus.edu.sg/NPASS/ | http://bidd2.nus.edu.sg/CMAUP/index.html |
| Contents and main features for COVID-19 investigations | Including herbs, ingredients and ADME properties, compound-target-disease interaction etc. | Including formulas, herbs, ingredients, gene targets, and related pathways or diseases. | Including formulas, herbs, ingredients, targets and diseases; drug targets and disease genes/proteins interactions etc. | Including massive descriptive information on herbs, TCM symptoms, MM symptoms, ingredients, targets, and diseases. Pairwise relationships among all these six types of components through direct association or indirect statistical inference. | Including natural products, organisms, and together with activity records on targets. | Including medicinal plants, molecular, target proteins, Gene Ontology, KEGG pathways and diseases. |
| Means of database-building | Manually collected (499 herbs registered in Chinese pharmacopoeia (2010), with a total of 12144 chemicals) and database integration. | Manually collected and integration of database (MedChem Studio, HPO, OMIM, DisGeNET and ORPHANET). | Data mining and integration of database (TCM@Taiwan, TCM-ID, DrugBank and OMIM). | Data mining and integration of database (UMLS, TCMID, TCM-ID, TCMSP, HIT, HPO, DrugBank, OMIM, Mesh, Orphanet and NCBI). | Data mining and integration of database (TCM-ID, TCMID, TCM@TaiWan, TCMSP, UNPD, TM-MC, TTD, TarNet, ChEBI, etc.). | Data mining and integration of database (ChEMBL, NPASS and TTD). |
| Latest update | 05/31/2014 | 10/26/2018 | 10/20/2016 | 10/31/2018 | 04/01/2018 | 2018 |
| Frequency | 73 (80) | 12 (80) | 9 (80) | 5 (80) | 3 (80) | 2 (80) |

| Database | YATCM | TCM-PTD | TCM-ID | TM-MC | NPB | CHEM-TCM |
|---|---|---|---|---|---|---|
| Website | http://cadd.pharmacy.nankai.edu.cn/yatcm/home | http://pharminfo.zju.edu.cn/ptd/ | http://tcm.cz3.nus.edu.sg/group/tcm-id/tcmid.asp | http://informatics.kiom.re.kr/compound/ | http://www.npbdb.net:8080/ | http://www.chemtcm.com/ |
| Contents and main features for COVID-19 investigations | Including TCM formulas, herbs, ingredients, definite or putative protein targets, pathways, and diseases. | Including detailed information of TCM, ingredients, FDA-approved drugs and targets. | Including formulas, herbs, ingredients, molecular structure and properties, therapeutic and side effects, clinical indication and application, and related matters, etc. | Including information on the constituent compounds of medicinal materials in Northeast Asia traditional medicine. Medicinal materials and compounds interactions etc. | Including the information (targets or activities etc.) of natural product in a wider range of disciplines. | Including chemical identification, botanical information, predicted activity against common Western therapeutic targets, and estimated molecular activity according to traditional Chinese herbal medicine categories. |
| Means of database-building | Manually collected and integration of database (TCMID, TCM@Taiwan, TCMSP, TTD, ChEMBL and KEGG database). | N/A. | Manually collected information on medicinal materials and their chemical compounds from MEDLINE and PMC. | Manually collected TCM classics and related research articles from National Library of Medicine. | N/A. | N/A. |
| Latest update | 11/23/2018 | 08/02/2012 | N/A | 12/03/2018 | 2020 | 10/2011 |
| Frequency | 1 (80) | 1 (80) | 0 (80) | 0 (80) | 0 (80) | 0 (80) |

*N/A: No information was retrieved.

2

## Author contributions

Yu-Xi Huang collected and analyzed the data. Shi-Jun Yue directed the research. Yu-Xi Huang, Wen-Xiao Wang, Sai Zhang, and Shi-Jun Yue wrote the manuscript. Shi-Jun Yue and Yu-Ping Tang reviewed and revised the manuscript.

## Declaration of Competing Interest

The authors declared that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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## 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.2020.105046.

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