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Evaluating the Traditional Chinese Medicine (TCM) Officially Recommended in China for COVID-19 Using Ontology-Based Side-Effect Prediction Framework (OSPF) and Deep Learning

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ABSTRACT

Ethnopharmacological relevance: The novel coronavirus disease (COVID-19) outbreak in Wuhan has imposed a huge influence in terms of public health and economy on society. However, no effective drugs or vaccines have been developed so far. Traditional Chinese Medicine (TCM) has been considered as a promising supplementary treatment of this disease due to its clinically proven performance in many severe diseases, like severe acute respiratory syndrome (SARS). Meanwhile, many reports suggest that the side-effects (SE) of TCM prescriptions cannot be ignored in treating COVID-19 as it often leads to dramatic degradation of the patients’ physical condition. Systematic evaluation of TCM regarding its latent SE becomes a burning issue.

Aim: In this study, we used an ontology-based side-effect prediction framework (OSPF) developed from our previous work and Artificial Neural Network (ANN)-based deep learning, to evaluate the TCM prescriptions officially recommended by China for the treatment of COVID-19.

Materials and methods: The OSPF developed from our previous work was implemented in this study, where an ontology-based model separated all ingredients in a TCM prescription into two categories: hot and cold. A database was created by converting each TCM prescription into a vector which contained ingredient dosages, corresponding hot/cold attribution and safe/unsafe labels. This allowed for training of the ANN model. A safety indicator (SI), as a complement to SE possibility, was then assigned to each TCM prescription. According to the proposed SI, from high to low, the recommended prescription list could be optimized. Furthermore, in interest of expanding the potential treatment options, SIs of other well-known TCM prescriptions, which are not included in the recommended list but are used traditionally to cure flu-like diseases, are also evaluated via this method.

Results: Based on SI, QFPD-T, HSBD-F, HSBD-F, SF-ZSY, and HSYF-F were the safest treatments in the recommended list, with SI scores over 0.8. PESP, QYLX-F, JHQG-KL, SFJD-JN, SHL-KFY, PESP1, XBJ-ZSY, HSZF-F, PSSP2, FFTS-W, and NHSQ-W were the prescriptions most likely to be unsafe, with SI scores below 0.1. In the additional lists of other TCM prescriptions, the indicators of XC-T, SQRS-S, CC-J, and XFBF-F were all above 0.8, while QF-Y, XZXS-S, BJD-J, and XOJ-T’s indicators were all below 0.1.

Conclusions: In total, there were 10 TCM prescriptions with indicators over 0.8, suggesting that they could be considered in treating COVID-19, if suitable. We believe this work could provide reasonable suggestions for choosing proper TCM prescriptions as a supplementary treatment for COVID-19. Furthermore, this work introduces a novel and informative method which could help create recommendation list of TCM prescriptions for the treatment of other diseases.
1. Introduction

The novel coronavirus disease (COVID-19) outbreak in Wuhan City has now spread worldwide, affecting more than 28 million people, with over 900,000 deaths reported (World Health Organization, 2020). Though it is suggested that the fatality rate of COVID-19 is relatively low compared to other infamous infectious diseases, the high contagiousness of this disease has created a formidable challenge. This has provoked a serious response from many governments all over the world, especially China (Zhao et al., 2020). Additionally, although some drugs seem to be promising in the treatment of COVID-19, no drug has yet been officially confirmed to be safe and effective in curing the disease (Yu et al., 2020). This situation needs to change in order to block and eliminate the spread of COVID-19.

In effort to put forth solutions, Traditional Chinese Medicine (TCM) has been considered as a prospective supplementary treatment, due to its proven clinical performance in treating many chronic diseases, mental disorders, and even SARS (Hao et al., 2017; Kim et al., 2008; Ren et al., 2019; Xiang et al., 2019). The Chinese government and other official institutes have published a list of TCM prescriptions recommended for each disease stage of the COVID-19 infection (released by National Health Commission & National Administration of Traditional Chinese Medicine, on March 3, 2020). However, there is a lack of reasonable and reliable criteria for evaluating TCM. Moreover, as there are many side effects (SE) reported in its application, it is recommended to take into account the SIs of TCM prescriptions and products. This is especially important in treating COVID-19, which could lead to dramatic degradation of the patients’ physical condition.

Artificial Intelligence (AI) has been widely applied to tasks that aim to identify features among many relationship-unknown objects (Krittanawong et al., 2017; Lecun et al., 2015). As one emerging technology of Artificial Neural Network (ANN) is becoming increasingly mature in describing relationships among pairwise data (Zhang et al., 2020). Furthermore, this technology has already provided a suitable approach towards high-accuracy TCM SI prediction with an ontology-based prediction model (Yao et al., 2019). Utilizing deep learning, recent research have also predicted possible modern antiviral drugs for COVID-19 (Beck et al., 2020).

In this work, by combining the deep learning method and SI prediction, we employed an ontology-based side-effect prediction framework (OSPF) to evaluate TCM prescriptions that are officially recommended for COVID-19 in China. We then reorganized the recommended prescription list based on proposed SI values. Moreover, in effort to expand potential treatment options, we also examine the safety of other well-known TCM prescriptions which are found in traditional flu-treatment books, but not in the recommended list of treating COVID-19. We believe this work will provide reasonable suggestions for choosing proper TCM prescriptions which might function as supplementary treatments for COVID-19. This work also provides a novel and informative approach to curating a more reasonable recommendation list of TCM prescriptions for the treatment of other diseases.

2. Methods

An OSPF, developed in our previous work, was implemented for evaluation purposes where each medicine component (an herb, mineral, etc.) in a TCM compound prescription (CP) was classified into several categories, such as “hot”, “cold”, “towards heart”, and “towards kidney” (Wang et al., 2020). The classification was inspired by an ontology-based theory (Zhou et al., 2004), where the categories like “hot” or “cold” were considered as the fundamental ontology items for describing attributes of TCM medicines. In other words, in the strategy of OSPF, TCM components in compounds are summarized as attribution labels. For example, the herb GUIZHI (Cinnamomum cassia Presl) is generalized as a group of labels including “hot”, “neutral”, and “towards heart”.

Concomitantly, we collected information from the TCM drug datasets that reportedly cause major SE (Yao et al., 2019). As a complement, a group of TCM CPs coming from the ancient and prestigious TCM book, Shanghanzabinglun, was regarded as safe. To be more specific, 264 TCM CPs without side effects reported in the TCM books were recognized as the non-SE prescriptions, and the 73 SE-causing TCM CPs are introduced as complementary data.

As shown in Fig. 1, by considering a group of labels, one compound prescription could be vectorized as a group of data by the Bag-of-Word (BOW) model (Harris, 1954). In order to construct such a model, we first build a complete dictionary \( B = \{ h_1, h_2, \ldots, h_n \} \) with size \( n \), containing \( n \) names for all the ingredients in our TCM CP dataset. Then, each TCM CP can be represented by a different vector \( B \) with the same length. The ith element in the vector Bis the dosage of this herb, with negative, positive, or neutral prefixes representing the attribute. In this work, we assume that all the prescriptions are independent of each other, which means...
Table 1: Cross-reference of Chinese and English names of TCM prescriptions used in this study. The scientific names of all botanical plants are listed in the supplemental material.

| Index | Chinese Name | Hanyu Pinyin | Abbreviation |
|-------|--------------|--------------|--------------|
| 1     | 桑菊感冒片   | Sangju ganmaopian | SJ-GMP |
| 2     | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 3     | 牛黄清心丸   | Niuhuangqingxin wan | NHQ-W |
| 4     | 桑菊感冒片   | Sangju ganmaopian | SJ-GMP |
| 5     | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 6     | 牛黄清心丸   | Niuhuangqingxin wan | NHQ-W |
| 7     | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 8     | 牛黄清心丸   | Niuhuangqingxin wan | NHQ-W |
| 9     | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 10    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 11    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 12    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 13    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 14    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 15    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 16    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 17    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 18    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 19    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 20    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 21    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 22    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 23    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |
| 24    | 桂枝汤冲剂   | Guizhitang chongji | GZT-CJ |

Fig. 2. Prediction results of the TCM safety indicator (SI) in the group of (a) officially recommended list and (b) other common prescriptions in treating flu-like diseases.

3. Result and discussion

A list of officially recommended TCM CPs to treat COVID-19 as well as their associated side effects were digitalized into vectors of BOW and input into the well-trained ANN. The outputs of the ANN consisted of indicators, ranging from 0 to 1, representing the predicted safety possibilities of corresponding TCM CP inputs. We also evaluated the SIs of three common prescriptions in treating COVID-19, Qingfei Paifu Decoction (QPFD-P), Huashi Baidu Formula (HSBD-F), and Xuanfei Baidu Formula (XFBF-F).

Table 1 lists the officially recommended TCM and other popular CPs currently used to treat similar symptoms. The scientific names of all botanical plants within these CPs are listed in the supplemental material. In this paper, abbreviations are applied to simplify descriptions where the suffixes -GM, -K, -F, -L, -S, -Y, -T, -W, and -mean table, oral solution, drug granules, capsule, injection, soup, pill, and powder/solution, respectively.

Finally, methods of network pharmacology were adopted to analyze the reasonability of SIs from an OSPF on a microscopic level. We first constructed an ingredient-target network \( t = (v, e) \) for each of the TCM CPs, where \( v \) represents a set of nodes in \( t \), and \( e \) is a set of edges in \( t \). Then, two traditional nodal measures between \( b_k \) and \( d_k \) were calculated for each network, \( \delta \) where \( j \in \{1, 2, \ldots, |V|\} \) and \( V = U_{i=1}^{12} \). Next, the SI of each ingredients-target network \( t \) was calculated by the previously trained ANN model. Next, we calculated the Spearman correlation coefficient between all SIs \( S = \{s_i\}_{i=1}^{12} \) and the nodal measures \( D = (d_j)_{j=1}^{12} \) or \( Be = (b_e)_{e=1}^{12} \) on each node in \( V \) to find the latent ingredients and targets which may be related to the SI of a TCM CP.
were all below 0.2. Previous research has found that SHL-KFY and JHQG-KL do show side effects, which is consistent with our prediction (Chinese Pharmacists Association Therapeutic Drug Monitoring Pharmacist Branch, 2020; Niu et al., 2016; Yang wei, 2002). Moreover, a study analysis of 101 clinical samples revealed that HXZQ-S causes side effects including red hot and anaphylactic shock (Liu, 2017).

Based on these results, a reorganized list is given in Fig. 3 based on averaged SI scores, where XC-T had the highest SI and KBD-CJ had the lowest. In total, there were seven TCM prescriptions with indicators over 0.8 suggested to be considered first in treating COVID-19, if suitable.

Training loss and accuracy of the ANN model were recorded to check the overfitting issue. As illustrated in Fig. 4, training loss and accuracy of the training data showed opposite trends. The accuracy of training data gradually increased to around 0.95 as the training loss decreased to around 0.15, rendering the ANN model acceptable. The trend suggested that the more samples that are applied to the model, the closer the prediction of the model and data distribution in the training set would be. As a result, the model will provide an accurate prediction capability. Some important parameters, such as sensitivity rate, specificity rate, and the macro-F1 score of the trained ANN model, which were used for SI prediction, are provided in Table 2.

Fig. 5 specifically shows the SI scores of 12 TCM CPs from the Chinese Seventh Edition of the Diagnosis and Treatment, which are calculated with and without the category labels. In this work, a Wilcoxon rank-sum test was used to examine whether there was a significant difference between the two results (Wilcoxon, 1945). It is obvious that, for NHSQ-W, SRYF-F, QYLF-F, and QYLX-F, the prediction results are opposite. Nevertheless, for SDYF-F, NBWT-F, and FPQX-F, the results have a non-negligible difference. Therefore, it is of great significance to take category labels into account, in the SI evaluation (p < 0.05, BF corrected).

As illustrated in Fig. 6, taking 12 prescriptions from the Seventh Edition of the Diagnosis and Treatment as an example, it is clear that the ingredients of CPs play roles in related biological functions via targets,
but the connection between the SE of a TCM CP and its ingredient-target relationship is still unclear. In detail, the SIs and each nodal measure of pharmacology networks derived from the corresponding CP are significantly relevant ($p < 0.05$), as shown in Table 3. A strong correlation indicates that the SI from our model can be interpreted as well, to some extent, by the pharmacological ingredients. This means the method used in this work can be supported by network pharmacology.

### 4. Conclusion

To conclude, this work provides an approach to the evaluation of TCM prescriptions included in the officially recommended list, as well as other well-known prescriptions for treating flu-like diseases. This work was conducted using OSPF and ANN-based deep learning methods. After training and testing the ANN model, results showed that QFPD-T, HSBD-F, FMSP, GCT-CJ, SF-ZSY, HSYF-F, XC-T, SQRS-S, CC-J, and XFBD-F were all recommended because of their SI scores over 0.8. Meanwhile, PESP, QYLX-F, JHQG-KL, SFJD-JN, SHL-KFY, PESP1, XBJ-ZSY, HSZF-F, PSSP2, FFTS-W, NHSQ-W, QF-Y, XZXS-S, BJ-S, KBD-CJ, and QWJD-T were not suggested to be used primarily because of their low scores. This work provided a reasonable suggestion for choosing proper TCM prescriptions as supplementary treatment for COVID-19. This work also provided a novel and informative approach to the assessment of a reasonable recommendation list of TCM prescriptions for other diseases.

### Author contributions

Z.W. conceived the idea and wrote the main manuscript text and prepared all figures. L.L. established the artificial model and run the code. Z.W. and L.L. contributed equally to this work. M.S. and J.S. collected the data used in this work. J.Y., M.S., and J.S. prepared the table and revise the paper manuscript. Y.Y. supervised the whole procedure of this study and provided the fund. All authors discussed the results and reviewed the manuscript.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2021.113957.

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