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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: Novel coronavirus disease (COVID-19) outbroke in Wuhan has imposed a huge influence onto the society in term of the public heath and economy. However, so far, no effective drugs or vaccines have been developed. Whereas, the Traditional Chinese Medicine (TCM) has been considered as a promising supplementary treatment for the disease owing to its clinically proven performance on many diseases even like severe acute respiratory syndrome (SARS). Meanwhile, many side-effect (SE) reports suggest the SE of the TCM prescriptions cannot be ignored in curing the COVID-19, especially because COVID-19 always simultaneously leads to dramatic degradation of the patients' physical condition. How to evaluate the TCM regarding to their latent SE is a urgent challenge.

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

Materials and methods: Firstly, we adopted the OSPF developed in our previous work, where an ontology-based model separate all the ingredients in a TCM prescription into two categories: hot and cold. Then, we established a database by converting each TCM prescription into a vector containing the ingredient dosage and the according hot/cold attribution as well as the safe/unsafe label. And, we trained the ANN model using this database, after which a safety indicator (SI), as the complementary percentage of side-effect (SE) possibility, is then given for each TCM prescription. According to the proposed SI from high to low, we re-organize the recommended prescription list. Secondly, by using this method, we also evaluate the safety indicators of some other famous TCM prescriptions that are not in the recommended list but are used traditionally to cure flu-like diseases for extending the potential treatments.

Results: Based on the SI generated in the ANN model, FTS, PMSP, and SF are the safest ones

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in recommended list, which all own a more-than-0.8 SI. Whereas, JHQG, LHQW, SFJD, XBJ, and SHL are the prescriptions that are most likely unsafe, where the indicators are all below 0.2. In the extra list, the indicators of XC, XQRS, CC, and CHBX are all above 0.8, and at the meantime, XZXS, SJ, QW, and KBD's indicators are all below 0.2.

Conclusions: In total, there are seven TCM prescriptions which own the indicators more than 0.8, suggesting these prescriptions should be considered firstly in curing COVID-19, if suitable. We believe this work will provide a reasonable suggestion for the society to choose proper TCM as the supplementary treatment for COVID-19. Besides, this work also introduces a pilot and enlightening method for creating a more reasonable recommendation list of TCM to other diseases.

1. Introduction

It has been reported that the novel coronavirus disease (COVID-19) originated in Wuhan City has infected more than 12,000 people all over the world so far, with more than 200 death reported (Kofi Ayittey et al., 2020). Although it is suggested that the fatality rate of COVID-19 is relatively low compared to other famous infectious diseases, the high reproduction number of this disease has created a formidable challenge towards blocking this super-flu, and hereby, aroused serious response of many countries' governments all over the world, especially Chinese government (Zhao et al., 2020). Additionally, although some drugs seem to be promising in the treatment, up to now it has not been officially confirmed that there is a vaccine or drug could be safely used to effectively cure the disease (Yu et al., 2020). This situation further hinders blocking and eliminating the spread of COVID-19.

In this sense, Traditional Chinese Medicine (TCM) starts to be considered as a prospective supplementary treatment, owing to its proven clinical performance in curing many chronic diseases, mental disorders, and even severe acute respiratory syndrome (SARS) (Hao et al., 2017; Kim et al., 2008; Ren et al., 2019; Xiang et al., 2019). Therefore, Chinese government and other official institutes have published a list of the TCM prescriptions recommended for each disease stage of the COVID-19 infected people ("Diagnosis and treatment of pneumonia caused by coronavirus (edition 4)," 2020; Lu, 2020). However, it still remains a critical problem which is how to evaluate the TCM in a reasonable basis. Moreover, because of many SE reports in TCM application, it is recommended to take into account the SE occurrence possibility of TCM prescriptions and products, especially in curing the COVID-19 which always simultaneously leads to dramatic degradation of the patients' physical condition.

On the other hand, Artificial Intelligence (AI) has been widely used in the tasks that require knowing features among lots of relationship-unknown objects (Krittanawong et al., 2017; Lecun et al., 2015). And, as one emerging technology of AI, the Artificial Neural Network (ANN) is getting more and more mature as well in describing the relationships between each part of the paired data (Zhang et al., 2020). Furthermore, this technology has already successfully provided a suitable approach towards high-accuracy TCM SE prediction based on an ontology-based prediction model, suggesting it is of great worth to adopt this method in predicting TCM SE occurrence possibility (Yao et al., 2019). In addition, research works that predict potential available modern antiviral drugs for COVID-19 using deep learning have

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been done recently (Beck et al., 2020).

In this paper, by taking advantage of deep learning method, we use an ontology-based SE prediction framework (OSPF) developed in our previous work to evaluate the TCM prescriptions that are officially recommended in China for COVID-19, in the basis of SE prediction. According to the proposed SI from high to low, we re-organize the recommended prescription list. Moreover, we also exam the safety of some other famous TCM prescriptions that are not in the recommended list but in traditional flu-treatment books for the purpose of enriching the potential treatments. We believe this work will provide a reasonable suggestion for the society to choose proper TCM as the supplementary treatment for COVID-19. Besides, this work also provides a pilot and enlightening method of creating a more reasonable recommendation list of TCM in the treatment of other diseases.

2. Method

An OSPF developed in our previous work in introduced into the evaluation. In this model, each medicine component (an herb, mineral, or etc.) in a TCM compound prescription is classified into one out of two categories based on an ontology-based theory, where hot and cold are considered as two fundamental ontology items to describe the attributes of TCM medicines. By considering the dosage of each component, one compound prescription could be digitalized as a group of data each item inside containing the name of the herb, category name of this herb (hot or cold), and the dosage of the herb. This dataset could be associated with labels that represent if the drug causes the non-negligible SE according to the clinic reports (Yao et al., 2019). Meanwhile, a group of TCM prescriptions coming from the ancient prestigious TCM book *Shanghanzebinglun* are introduced as the standard prescriptions that are relatively safe. More information of the OSPF and the database could be found in our previous work (Yao et al., 2019).

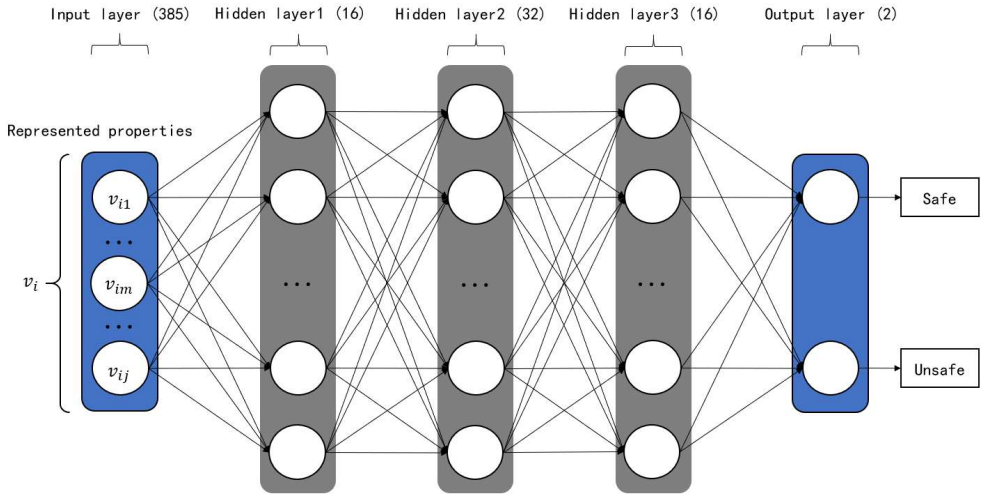

Fig. 1. The schematic structure of the ANN used in this work

An ANN model is then established to learn the latent relationship between the structures of TCM prescriptions and the SE occurrence possibility. In detail, as shown in Fig. 1, the ANN contains 5 layers where the input layer contains 385 units for receiving the Bag of Word (BOW) vector. The BOW is a dictionary including the name of all the TCM drug ingredients. And, the BOW vector has the information of dosage and attributes. Besides, the output layer contains

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two units for yielding the prediction. The three hidden layers that totally have more than 60 units are used to sense and remember the complex relationships between attributes of pharmaceutical ingredients, such as Cold and Hot, and their side effects in this prescription.

In order to train the ANN model above mentioned, 10-fold-cross-validation is applied, and appropriate parameters are selected. The previous dataset is randomly separated into 10 sub-datasets. In each procedure, one set out of these 10 separations is randomly picked out as a test set, the remained sets are regarded as training sets. Then, the training sets and the test sets are input to the ANN in sequence. By repeating this procedure 10 times, the accuracy of test set in each procedure is recorded for yielding prediction results of our ANN model.

Using the same OSPF, a list of TCM prescriptions officially recommended is digitalized and input into the ANN that has been well trained as mentioned previously. The output of the ANN is an indicator with a range from 0 to 1 that represents the predicted completely safe possibility of the TCM input. The SE occurrence possibility could be considered as the complementary percentage of the completely safe possibility.

Table 1 lists out the TCM prescriptions that are used in this work. To simplify the description afterwards, the symbol representation is adopted, where the suffix GMP, KFY, KL/CJ, JN, ZSY, T, W, and S means tablet, oral solution, drug granules, capsule, injection, soup, pill, and powder/solution, respectively.

Table 1. The cross-reference of the Chinese and English name of the TCM prescriptions used in this work.

Index	Chinese Name	Hanyu Pinyin	English Name	Abbreviations
1	桑菊感冒片	Sangju ganmaopian	N.A.	SJ-GMP
2	芎芷香苏散	Xiongzhixiangsu san	N.A.	XZXS-S
3	加减羌活五积散	Jiajianqianghuowuji san	N.A.	JJQHWJ-S
4	百解散	Baijie san	N.A.	BJ-S
5	相传汤	Xiangchuan tang	N.A.	XC-T
6	顺气人参散	Shunqirenshen san	N.A.	SQRS-S
7	柴陈煎	Chaichen jian	N.A.	CC-J
8	柴胡半夏汤	Chaihubanxia tang	N.A.	CHBX-T
9	清肺饮	Qingfei yin	N.A.	QF-Y
10	清瘟解毒汤	Qingwenjiedu tang	N.A.	QWJD-T
11	藿香正气水	Huoxiangzhengqi shui	N.A.	HXZQ-S
12	抗病毒冲剂	Kangbingdu chongji	N.A.	KBD-CJ
13	金花清感颗粒	Jinhuaqinggan keli	N.A.	JHQG-KL
14	连花清瘟胶囊	Lianhuaqingwen jiaonang	N.A.	LHQW-JN
15	疏风解毒胶囊	Shufengjiedu jiaonang	N.A.	SFJD-JN
16	防风通圣丸	Fangfengtongsheng wan	N.A.	FFTS-W
17	初期方子	Chuqifangzi	Prescription for early stage of pneumonia	PESP

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18	中期方子	Zhongqifangzi	Prescription for middle stage of pneumonia	PMSP
19	血必静注射剂	Xuebijing zhusheji	N.A.	XBJ-ZSJ
20	重症期方子 1	Zhongzhengqifangzi1	Prescription for severe stage of pneumonia No.1	PSSP1
21	重症期方子 2	Zhongzhengqifangzi2	Prescription for severe stage of pneumonia No.2	PSSP2
22	参附注射液	Shenfu zhusheye	N.A.	SF-ZSY
23	生脉注射液	Shengmai zhusheye	N.A.	SM-ZSY
24	恢复期方子		Prescription for recovery stage of pneumonia	PRSP
25	双黄连口服液	Shuanghuanlian koufuye	N.A.	SHL-KFY

3. Result and discussion

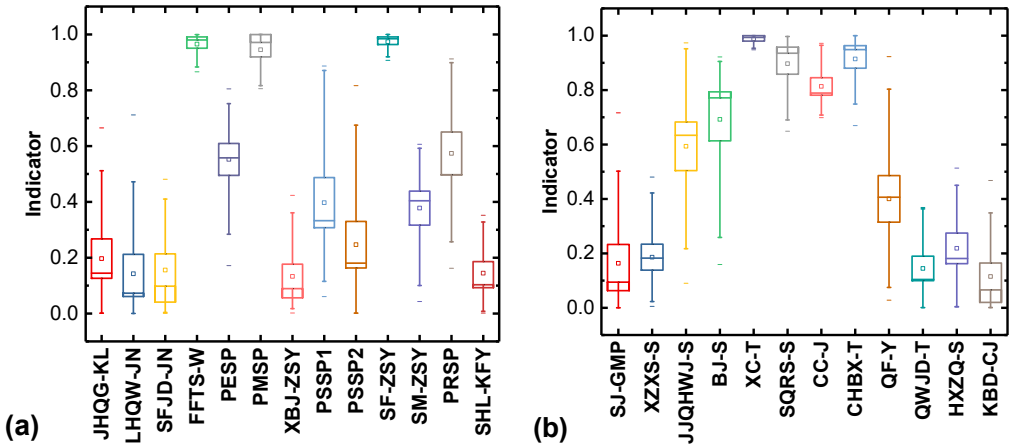

Fig. 2. The prediction results of the TCM safety indicator (SI) in the group of (a) officially recommended list and (b) other famous prescriptions in curing flu-like diseases.

Fig. 2 (a) and (b) show the calculated SI of the recommended list and the supplementary list respectively. Every data box contains ten result points, where the tiny square represents the mean value of these ten data. As indicated in the figure, the TCM prescriptions FFTS, PMSP, and SF are the safest ones in recommended list, which all own a more-than-0.8 SI. Whereas, JHQG, LHQW, SFJD, XBJ, and SHL are the prescriptions that are most likely unsafe, where the indicators are all below 0.2. Recently, an intensive debate is occurring in Chinese social media about whether SHL is proper TCM for COVID-19 disease. The results in this work suggests SHL should not be the treatment in the priority. Besides, regarding to other famous

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prescriptions in curing flu-like diseases, the indicators of XC, XQRS, CC, and CHBX are all above 0.8, and at the meantime, XZXS, SJ, QW, and KBD's indicators are all below 0.2.

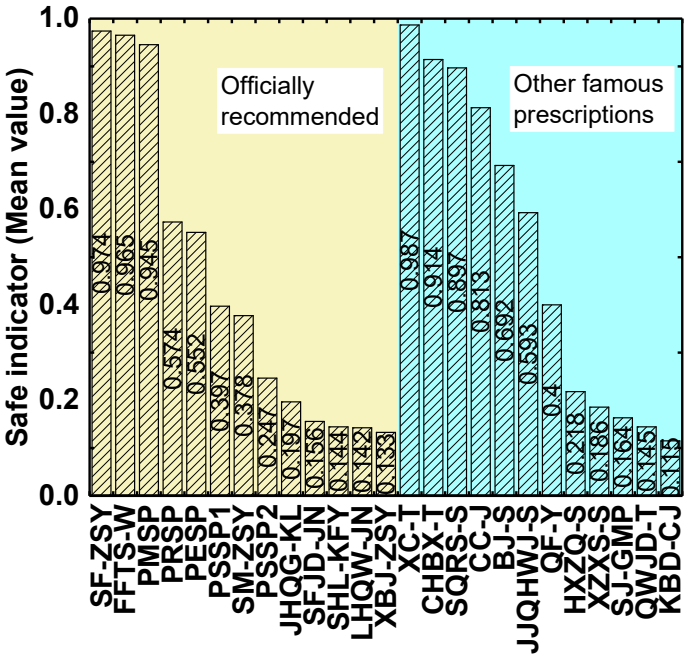

Fig. 3. The re-organized list of the TCM prescriptions studied in this work based on the predicted mean value of the SI.

Based on these results, a re-organized list is given in Fig. 3 based on the mean of the SI, where the XC-T has the highest SI and the KBD-CJ has the lowest one. In total, there are seven TCM prescriptions which own the indicators more than 0.8, suggesting these prescriptions should be considered firstly in curing COVID-19, if suitable.

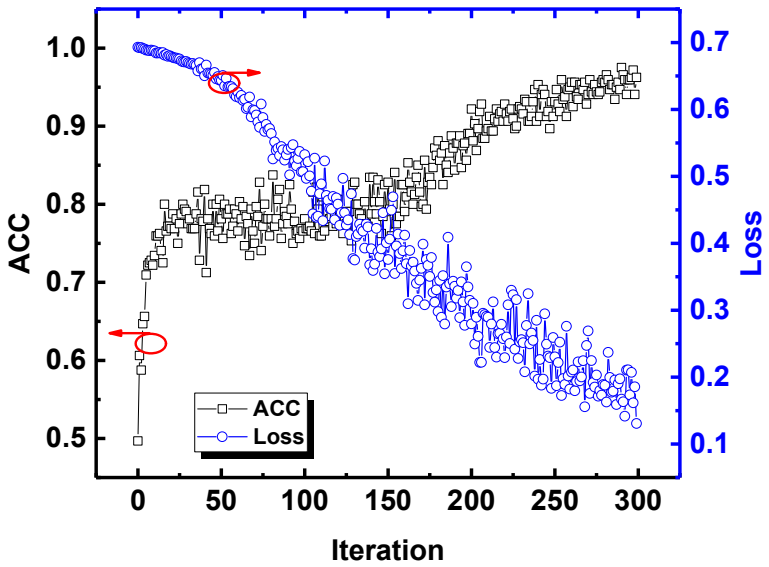

Fig. 4. The ACC and loss of the model versus the iteration number.

Besides, the training loss and accuracy of the ANN model is recorded to check if there is overfitting issue. Illustrated in Fig. 4, the training loss and the accuracy of the training data

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show the opposite trend. The accuracy of the training data gradually increases to around 0.95 as the training loss decreases to around 0.15, rendering the ANN model used in this paper is reasonable. The trend suggests that as more and more samples are applied to the model, the prediction of the model would be closer to the data distribution in the training set in which case the model will provide a more and more accurate prediction capability.

4. Conclusion

To conclude, this paper gives a try evaluate the TCM prescriptions in officially recommended list and other famous prescriptions in curing flu-like diseases, using OSPF and ANN-based deep learning method. After the training and testing the ANN model, the results show that FFTS, PMSP, SF, XC, XQRS, CC, and CHBX are all recommended regarding to their more-than-0.8 SI. While, JHQG, LHQW, SFJD, XBJ, SHL, XZXS, SJ, QW, and KBD are not suggested to be used firstly because of their low indicators. This work provides a reasonable suggestion for the society to choose proper TCM as the supplementary treatment for COVID-19. Besides, this work also provides a pilot and enlightening method of creating a more reasonable recommendation list of TCM in the treatment of other diseases.

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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. J.Y. 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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