Supplementary Information for Risk of drug-drug interactions in China's fight against COVID-19 and beyond

Qingpeng Zhang[1,2], Jiannan Yang[1], Daniel Dajun Zeng[3], Ian C.K. Wong[2]

1. Methods

We applied a deep learning-based DDI prediction model to identify the potential DDIs in addition to known DDIs. The deep learning model adopted a Graph Convolutional Network framework proposed by (Zitnik et al., 2018), and was trained by identifying the complex relationships of drugs based on the protein-protein interaction (PPI) network. The details are shown as follows

1.1. Datasets for Training

1.1.1. **Protein-protein interaction (PPI) network.** For our current study, we employed the same PPI network as in our previous research. This network comprises 614,970 interactions among 13,758 proteins and was sourced from two datasets, including (Cheng et al., 2019) and STRING (Szklarczyk et al., 2021).

1.1.2. **Drug-protein interactions (DPI).** The DPIs used in our study contains the interactions between western drugs and proteins, also Traditional Chinese medicines (TCM) drugs and their protein targets. For western drugs, we curated 29,419 drug-protein interactions from DrugBank (Wishart et al., 2018) and the dataset used in (Cheng et al., 2019), which covers 6,484 western drugs. And for TCM drugs, the DPI information comes from HERB (Fang et al., 2021) and Chinese Pharmacopoeia 2020 (https://www.bopuyun.com/pc/book/4?zch=seoggs,seooth), which contains 142,821 interactions covers 1,573 TCM drugs. We first collected their component herbs and find the related protein targets of these herbs and then aggregate all these protein targets together as the related proteins of certain TCM drug.

1.1.3. Drug-drug interactions (DDI). The training of the deep learning model for DDI prediction is performed on the western drugs. The negative drug-drug interactions (label is 1) are collected from DrugBank (Wishart et al., 2018) and DDInter (Xiong et al., 2022), which contains 592,986 negative interactions and 455,150 “unknown” and “positive” interactions among

4,446 drugs. Besides the negative DDIs, these public datasets also provide us with the "unknown" DDIs and "positive" DDIs, which we used as the negative label (0) during training.

1.2. Training on DDIs from Western medicines

1.2.1. Training

Based on the data we collected, we built a graph $G = (V, E)$, where V and E are the node set and edge set, respectively. The nodes V are the proteins and drugs, including both western drugs and TCM drugs. The edges E are the PPIs and DPIs among these nodes. The training of the deep learning model is performed on the western drugs since we have no DDI data for the TCM drugs. Specifically, given the adjacency matrix A of the graph, we first initialized the numeric representations $E \in \mathbb{R}^{N \times d}$ of all the nodes to a 64-dimional embeddings and then perform a 3-layer GCN to get the output. One layer of GCN is shown below:

$$E^{l+1} = \sigma_G\left(D^{-1}(A + I)D^{-1}E^l W^l\right), \quad (1)$$

where D is the diagonal node degree matrix, I is the identity matrix, σ_G is the activation function (relu) and, W^l is the learning weights at layer l.

Then, given the embeddings of two drugs D_1 and D_2, we utilized the inner product $\otimes$ and Softmax activation function σ to get the output:

$$\hat{y} = \sigma(D_1 \otimes D_2), \quad (2)$$

We treated the prediction of negative DDIs as a binary classification task and used a binary cross entropy loss

$$\mathbb{L} = \sum(-y \log \hat{y} - (1 - y) \log(1 - \hat{y})), \quad (3)$$

The parameters of the deep learning model are optimized by the Adam algorithm. For the hyper-parameters, we set the learning rate as 0.001, the dropout ratio as 0.1. The layer size of the 3-layer GCN are 64-128-64.

1.2.2. Performance

We introduced a 7-1-2 split ratio to split the dataset into training, validation, and test sets. We report the performance of our GCN model on the test dataset in Table S1. As shown in the table, our model achieved an AUC-ROC of 0.84, which indicates high performance in predicting negative DDIs.

Table S1. The performance of our GCN model on the test dataset.

Accuracy	Recall	Precision	AUC-ROC
0.74	0.84	0.66	0.84

1.3. Inferencing

We introduced the trained deep learning model trained to make inference on all the drug-drug pairs of 18 OTC drugs. Specifically, given two drugs, we get the embeddings of these two drugs and then applied equation (2) to get the probability of whether these two drugs will have negative DDI.

2. Results

Figure S1 presents the predicted probability of negative DDIs between a pair of drugs as a heatmap. Our GCN model utilizes the related protein information of each drug in a given drug pair, regardless of whether it belongs to TCM or Western medicine. Based on these proteins' specific topological information in the PPI network, the model generates a predicted probability of negative DDI, which represents the risk of negative DDI and is expressed as a numeric value between 0 and 1. A higher predicted probability indicates a greater risk of negative DDI. We label the drug pairs as high-risk if the predicted probability of DDI is over 50%. Among 18 drugs, we find 70 high-risk drug pairs. Specifically, there are 16 high-risk drug pairs between Western medicine drugs, 16 between TCM drugs, and 38 between Western medicine and TCM drugs. Among these high-risk drug pairs, only three pair were clinically verified (acetylcysteine-cetirizine, cetirizine- chlorpheniramine, aspirin-ibuprofen).

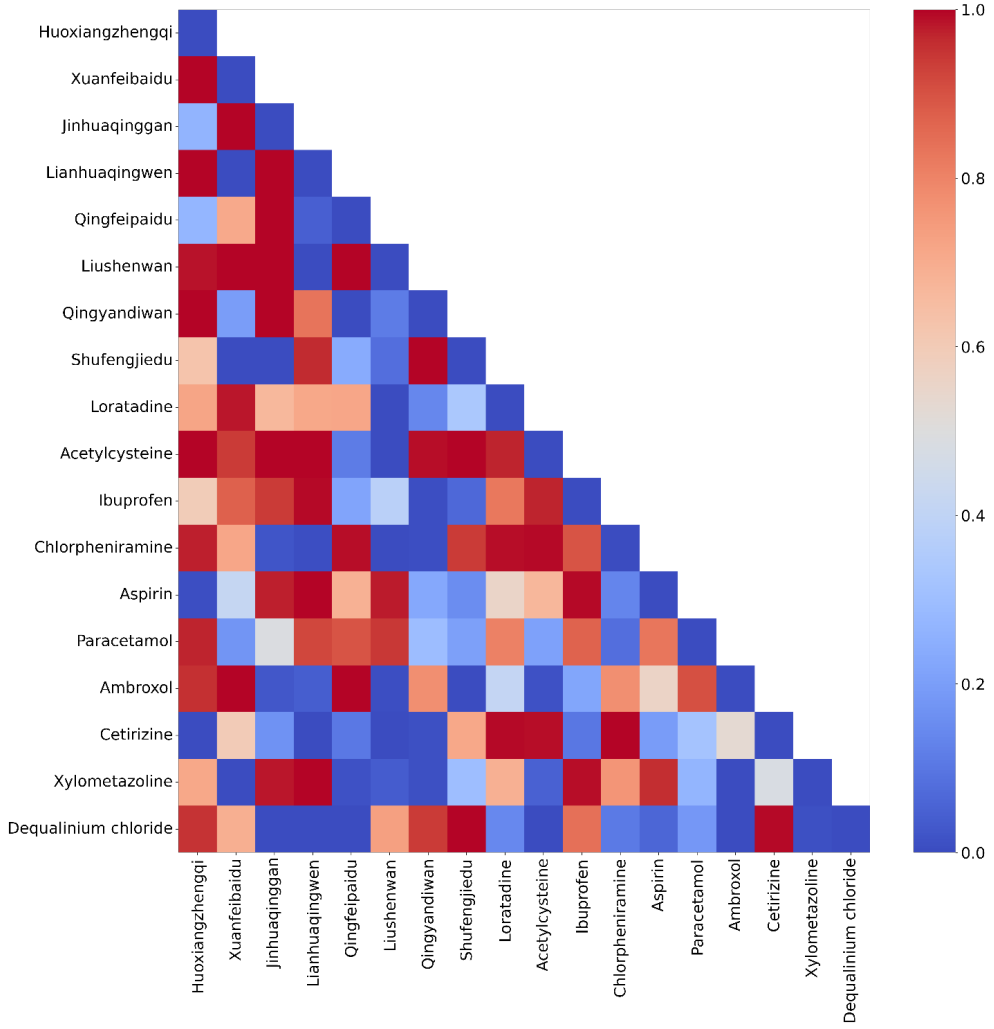

Figure S1. The heatmap of the predicted probability of negative DDIs between a pair of OTC drugs recommended by (National Health Commission of China, 2022b). TCM drugs are listed in the first 8 rows/columns and Western medicine drugs are listed in the rest. Within each category, drugs are aligned according to the probability of having DDIs with other drugs.

The predicted probability of the negative DDIs for all the drug-drug pairs among the 18 OTC drugs are shown in Table S2 below.

Table S2. The predicted probability of the negative DDIs for all the drug-drug pairs among the 18 OTC drugs.

Drug1	Drug2	$\hat{y}$	Drug1	Drug2	$\hat{y}$	Drug1	Drug2	$\hat{y}$
Paracetamol	Xuanfeibaidu	0.36	Lianhuaqingwen	Qingyandiwan	0.79	Qingyandiwan	Shufengjiedu	1.00
Paracetamol	Dequalinium chloride	0.06	Lianhuaqingwen	Liushenwan	0.00	Qingyandiwan	Qingfeipaidu	0.00
Paracetamol	Lianhuaqingwen	0.78	Lianhuaqingwen	Ibuprofen	0.84	Qingyandiwan	Xylometazoline	0.05
Paracetamol	Cetirizine	0.42	Lianhuaqingwen	Ambroxol	0.04	Qingyandiwan	Aspirin	0.57
Paracetamol	Huoxiangzhengqi	0.91	Lianhuaqingwen	Chlorpheniramine	0.31	Qingyandiwan	Loratadine	0.04
Paracetamol	Acetylcysteine	0.59	Lianhuaqingwen	Shufengjiedu	0.95	Qingyandiwan	Jinhuaqinggan	1.00
Paracetamol	Qingyandiwan	0.51	Lianhuaqingwen	Qingfeipaidu	0.04	Liushenwan	Ibuprofen	0.12
Paracetamol	Liushenwan	0.88	Lianhuaqingwen	Xylometazoline	1.00	Liushenwan	Ambroxol	0.04
Paracetamol	Ibuprofen	0.90	Lianhuaqingwen	Aspirin	0.98	Liushenwan	Chlorpheniramine	0.00
Paracetamol	Ambroxol	0.87	Lianhuaqingwen	Loratadine	0.41	Liushenwan	Shufengjiedu	0.07
Paracetamol	Chlorpheniramine	0.31	Lianhuaqingwen	Jinhuaqinggan	1.00	Liushenwan	Qingfeipaidu	1.00
Paracetamol	Shufengjiedu	0.04	Cetirizine	Huoxiangzhengqi	0.02	Liushenwan	Xylometazoline	0.00
Paracetamol	Qingfeipaidu	0.92	Cetirizine	Acetylcysteine	0.01	Liushenwan	Aspirin	0.45
Paracetamol	Xylometazoline	0.08	Cetirizine	Qingyandiwan	0.39	Liushenwan	Loratadine	0.30
Paracetamol	Aspirin	0.81	Cetirizine	Liushenwan	0.06	Liushenwan	Jinhuaqinggan	1.00
Paracetamol	Loratadine	0.48	Cetirizine	Ibuprofen	0.19	Ibuprofen	Ambroxol	0.41
Paracetamol	Jinhuaqinggan	0.21	Cetirizine	Ambroxol	0.08	Ibuprofen	Chlorpheniramine	0.64

Xuanfeibaidu	Dequalinium chloride	0.88	Cetirizine	Chlorphenirami ne	1.00	Ibuprofen	Shufengjiedu	0.08
Xuanfeibaidu	Lianhuaqingwe n	0.00	Cetirizine	Shufengjiedu	0.63	Ibuprofen	Qingfeipaidu	0.77
Xuanfeibaidu	Cetirizine	0.32	Cetirizine	Qingfeipaidu	0.36	Ibuprofen	Xylometazoline	0.77
Xuanfeibaidu	Huoxiangzheng qi	1.00	Cetirizine	Xylometazoline	0.40	Ibuprofen	Aspirin	0.96
Xuanfeibaidu	Acetylcysteine	1.00	Cetirizine	Aspirin	0.23	Ibuprofen	Loratadine	0.32
Xuanfeibaidu	Qingyandiwan	0.15	Cetirizine	Loratadine	0.86	Ibuprofen	Jinhuaqinggan	0.47
Xuanfeibaidu	Liushenwan	1.00	Cetirizine	Jinhuaqinggan	0.05	Ambroxol	Chlorpheniramin e	0.25
Xuanfeibaidu	Ibuprofen	0.06	Huoxiangzhengq i	Acetylcysteine	1.00	Ambroxol	Shufengjiedu	0.00
Xuanfeibaidu	Ambroxol	1.00	Huoxiangzhengq i	Qingyandiwan	1.00	Ambroxol	Qingfeipaidu	1.00
Xuanfeibaidu	Chlorphenirami ne	0.86	Huoxiangzhengq i	Liushenwan	0.98	Ambroxol	Xylometazoline	0.00
Xuanfeibaidu	Shufengjiedu	0.00	Huoxiangzhengq i	Ibuprofen	0.00	Ambroxol	Aspirin	0.12
Xuanfeibaidu	Qingfeipaidu	0.67	Huoxiangzhengq i	Ambroxol	0.99	Ambroxol	Loratadine	0.62
Xuanfeibaidu	Xylometazoline	0.00	Huoxiangzhengq i	Chlorphenirami ne	0.57	Ambroxol	Jinhuaqinggan	0.23
Xuanfeibaidu	Aspirin	0.03	Huoxiangzhengq i	Shufengjiedu	0.62	Chlorpheniramin e	Shufengjiedu	0.28
Xuanfeibaidu	Loratadine	1.00	Huoxiangzhengq i	Qingfeipaidu	0.25	Chlorpheniramin e	Qingfeipaidu	0.57
Xuanfeibaidu	Jinhuaqinggan	1.00	Huoxiangzhengq i	Xylometazoline	0.16	Chlorpheniramin e	Xylometazoline	0.56
Dequalinium chloride	Lianhuaqingwe n	0.00	Huoxiangzhengq i	Aspirin	0.01	Chlorpheniramin e	Aspirin	0.43
Dequalinium chloride	Cetirizine	0.44	Huoxiangzhengq i	Loratadine	0.99	Chlorpheniramin e	Loratadine	0.55
Dequalinium chloride	Huoxiangzheng qi	0.92	Huoxiangzhengq i	Jinhuaqinggan	0.22	Chlorpheniramin e	Jinhuaqinggan	0.04
Dequalinium chloride	Acetylcysteine	0.00	Acetylcysteine	Qingyandiwan	1.00	Shufengjiedu	Qingfeipaidu	0.21

Dequalinium chloride	Qingyandiwan	0.97	Acetylcysteine	Liushenwan	0.29	Shufengjiedu	Xylometazoline	0.07
Dequalinium chloride	Liushenwan	0.94	Acetylcysteine	Ibuprofen	0.11	Shufengjiedu	Aspirin	0.68
Dequalinium chloride	Ibuprofen	0.40	Acetylcysteine	Ambroxol	1.00	Shufengjiedu	Loratadine	0.72
Dequalinium chloride	Ambroxol	0.00	Acetylcysteine	Chlorphenirami ne	0.33	Shufengjiedu	Jinhuaqinggan	0.00
Dequalinium chloride	Chlorphenirami ne	0.67	Acetylcysteine	Shufengjiedu	1.00	Qingfeipaidu	Xylometazoline	0.05
Dequalinium chloride	Shufengjiedu	1.00	Acetylcysteine	Qingfeipaidu	0.94	Qingfeipaidu	Aspirin	0.76
Dequalinium chloride	Qingfeipaidu	0.00	Acetylcysteine	Xylometazoline	0.01	Qingfeipaidu	Loratadine	0.70
Dequalinium chloride	Xylometazoline	0.14	Acetylcysteine	Aspirin	0.08	Qingfeipaidu	Jinhuaqinggan	1.00
Dequalinium chloride	Aspirin	0.32	Acetylcysteine	Loratadine	0.44	Xylometazoline	Aspirin	0.83
Dequalinium chloride	Loratadine	0.01	Acetylcysteine	Jinhuaqinggan	1.00	Xylometazoline	Loratadine	0.65
Dequalinium chloride	Jinhuaqinggan	0.01	Qingyandiwan	Liushenwan	0.07	Xylometazoline	Jinhuaqinggan	1.00
Lianhuaqingwe n	Cetirizine	0.00	Qingyandiwan	Ibuprofen	0.06	Aspirin	Loratadine	0.43
Lianhuaqingwe n	Huoxiangzheng qi	1.00	Qingyandiwan	Ambroxol	0.18	Aspirin	Jinhuaqinggan	0.60
Lianhuaqingwe n	Acetylcysteine	0.68	Qingyandiwan	Chlorphenirami ne	0.03	Loratadine	Jinhuaqinggan	0.84

3. Discussion

In this study, we introduced a Graph Convolutional Network that leveraged knowledge of DDIs in Western medicine drugs to predict the risks of potential DDIs between TCMs and Western medicines. The identification of these DDIs sheds light on the potential for pharmacogenetic testing to guide clinical decision-making. Furthermore, our study highlights potential strategies to prevent or mitigate the risk of DDIs, such as dose adjustments, therapeutic drug monitoring, and drug substitution. However, it is important to note that most of the identified DDIs in our study (as shown in Figure S1 and Table S2) have yet to be clinically and preclinically validated. In future studies, we plan to conduct preclinical and clinical investigations to validate the drug-drug interactions identified in our study, particularly those with a high potential for adverse effects. Moreover, our model identified specific protein interactions between drug pairs, as shown in Figure 1 in the main text. This finding suggests the possibility of exploring the mechanisms underlying DDIs, such as the impact of drug metabolism and transporters on their pharmacokinetics and pharmacodynamics. We believe that future studies can build on these findings to further investigate the underlying biological mechanisms of DDIs. We hope these findings and recommendations will contribute to advancing our understanding of DDIs and ultimately improve patient safety and outcomes.

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