Supplementary Information for Elevated risk of drug-drug interactions while easing COVID-19 restrictions in China

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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

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.

1.3. 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 1 presents the predicted probability of negative DDIs between a pair of drugs as a heatmap. We label the drug pairs as high-risk if the predicted probability of DDI is over 90%. Among 18 drugs, we find 82 high-risk drug pairs. Specifically, there are 25 high-risk drug pairs between Western medicine drugs, 16 between TCM drugs, and 41 between Western medicine and TCM drugs. Among these high-risk drug pairs, only seven were clinically verified (acetylcysteine-cetirizine, acetylcysteine-loratadine, aspirin-ibuprofen, aspirin- xylometazoline, cetirizine-chlorpheniramine, cetirizine-loratadine, and chlorpheniramine-loratadine).

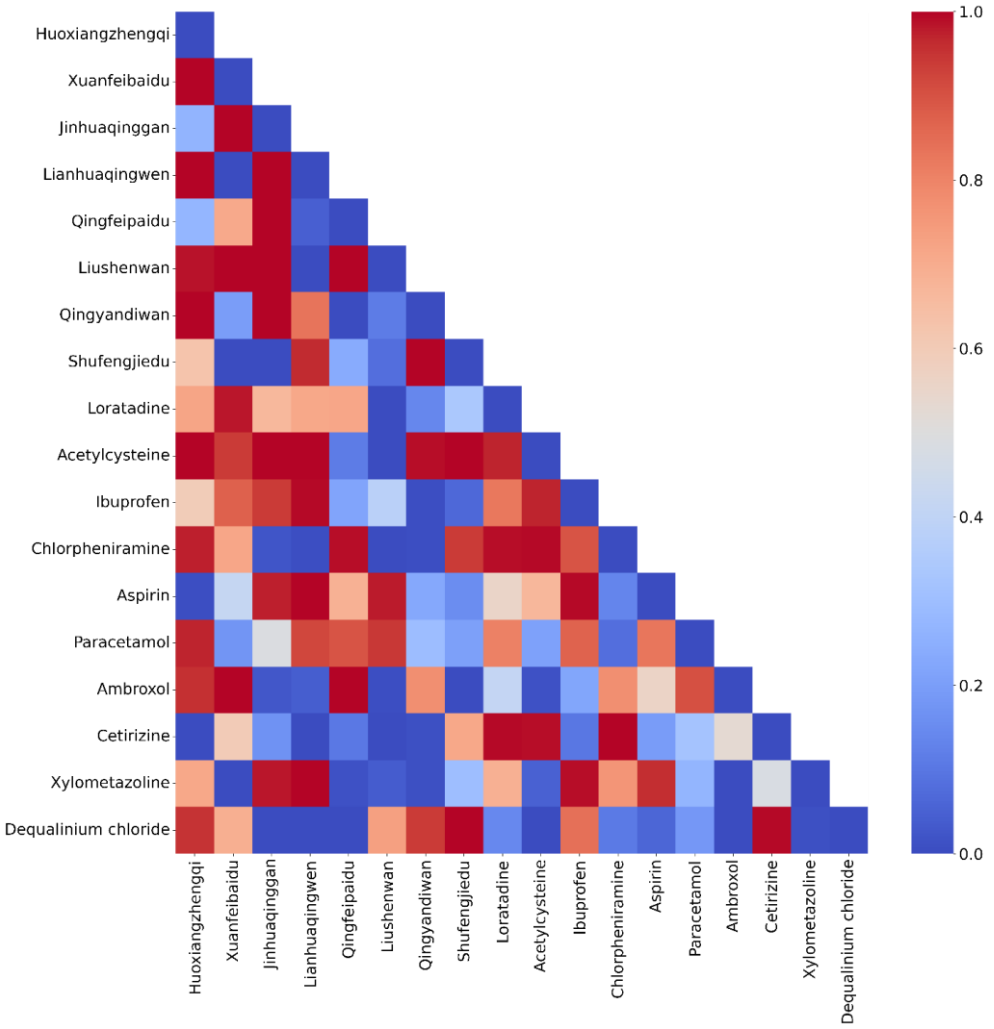

Figure 1. The heatmap of the predicted probability of negative DDIs between a pair of OTC drugs recommended by (National Health Commission of China, 2022b). TCM drugs are listed in the first 8 rows/columns and Western medicine drugs are listed in the rest. Within each category, drugs are aligned according 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 below.

Drug1	Drug2	$\hat{y}$	Drug1	Drug2	$\hat{y}$	Drug1	Drug2	$\hat{y}$
Jinhuaqinggan	Chlorpheniramine	0.02	Qingyandiwan	Aspirin	0.23	Aspirin	Ambroxol	0.56
Jinhuaqinggan	Paracetamol	0.49	Qingyandiwan	Qingfeipaidu	0.00	Aspirin	Acetylcysteine	0.67
Jinhuaqinggan	Qingyandiwan	1.00	Qingyandiwan	Xuanfeibaidu	0.20	Aspirin	Cetirizine	0.19
Jinhuaqinggan	Ibuprofen	0.94	Qingyandiwan	Xylometazoline	0.01	Aspirin	Shufengjiedu	0.15
Jinhuaqinggan	Dequalinium chloride	0.00	Qingyandiwan	Huoxiangzhengqi	1.00	Aspirin	Lianhuaqingwen	1.00
Jinhuaqinggan	Loratadine	0.67	Qingyandiwan	Ambroxol	0.78	Aspirin	Liushenwan	0.98
Jinhuaqinggan	Aspirin	0.97	Qingyandiwan	Acetylcysteine	0.99	Qingfeipaidu	Xuanfeibaidu	0.71
Jinhuaqinggan	Qingfeipaidu	1.00	Qingyandiwan	Cetirizine	0.01	Qingfeipaidu	Xylometazoline	0.01
Jinhuaqinggan	Xuanfeibaidu	1.00	Qingyandiwan	Shufengjiedu	1.00	Qingfeipaidu	Huoxiangzhengqi	0.27
Jinhuaqinggan	Xylometazoline	0.98	Qingyandiwan	Lianhuaqingwen	0.83	Qingfeipaidu	Ambroxol	1.00
Jinhuaqinggan	Huoxiangzhengqi	0.26	Qingyandiwan	Liushenwan	0.11	Qingfeipaidu	Acetylcysteine	0.11
Jinhuaqinggan	Ambroxol	0.02	Ibuprofen	Dequalinium chloride	0.84	Qingfeipaidu	Cetirizine	0.11
Jinhuaqinggan	Acetylcysteine	1.00	Ibuprofen	Loratadine	0.83	Qingfeipaidu	Shufengjiedu	0.24
Jinhuaqinggan	Cetirizine	0.17	Ibuprofen	Aspirin	0.99	Qingfeipaidu	Lianhuaqingwen	0.05
Jinhuaqinggan	Shufengjiedu	0.00	Ibuprofen	Qingfeipaidu	0.22	Qingfeipaidu	Liushenwan	1.00
Jinhuaqinggan	Lianhuaqingwen	1.00	Ibuprofen	Xuanfeibaidu	0.87	Xuanfeibaidu	Xylometazoline	0.00
Jinhuaqinggan	Liushenwan	1.00	Ibuprofen	Xylometazoline	0.99	Xuanfeibaidu	Huoxiangzhengqi	1.00
Chlorpheniramine	Paracetamol	0.08	Ibuprofen	Huoxiangzhengqi	0.60	Xuanfeibaidu	Ambroxol	1.00
Chlorpheniramine	Qingyandiwan	0.01	Ibuprofen	Ambroxol	0.22	Xuanfeibaidu	Acetylcysteine	0.94
Chlorpheniramine	Ibuprofen	0.90	Ibuprofen	Acetylcysteine	0.97	Xuanfeibaidu	Cetirizine	0.60
Chlorpheniramine	Dequalinium chloride	0.11	Ibuprofen	Cetirizine	0.10	Xuanfeibaidu	Shufengjiedu	0.00
Chlorpheniramine	Loratadine	0.99	Ibuprofen	Shufengjiedu	0.06	Xuanfeibaidu	Lianhuaqingwen	0.00
Chlorpheniramine	Aspirin	0.13	Ibuprofen	Lianhuaqingwen	0.99	Xuanfeibaidu	Liushenwan	1.00
Chlorpheniramine	Qingfeipaidu	0.99	Ibuprofen	Liushenwan	0.38	Xylometazoline	Huoxiangzhengqi	0.71
Chlorpheniramine	Xuanfeibaidu	0.72	Dequalinium chloride	Loratadine	0.14	Xylometazoline	Ambroxol	0.00
Chlorpheniramine	Xylometazoline	0.76	Dequalinium chloride	Aspirin	0.06	Xylometazoline	Acetylcysteine	0.05

Chlorpheniramine	Huoxiangzhengqi	0.97	Dequalinium chloride	Qingfeipaidu	0.00	Xylometazoline	Cetirizine	0.48
Chlorpheniramine	Ambroxol	0.78	Dequalinium chloride	Xuanfeibaidu	0.69	Xylometazoline	Shufengjiedu	0.30
Chlorpheniramine	Acetylcysteine	0.99	Dequalinium chloride	Xylometazoline	0.01	Xylometazoline	Lianhuaqingwen	1.00
Chlorpheniramine	Cetirizine	1.00	Dequalinium chloride	Huoxiangzhengqi	0.95	Xylometazoline	Liushenwan	0.04
Chlorpheniramine	Shufengjiedu	0.94	Dequalinium chloride	Ambroxol	0.00	Huoxiangzhengqi	Ambroxol	0.96
Chlorpheniramine	Lianhuaqingwen	0.00	Dequalinium chloride	Acetylcysteine	0.00	Huoxiangzhengqi	Acetylcysteine	1.00
Chlorpheniramine	Liushenwan	0.00	Dequalinium chloride	Cetirizine	0.99	Huoxiangzhengqi	Cetirizine	0.00
Paracetamol	Qingyandiwan	0.29	Dequalinium chloride	Shufengjiedu	1.00	Huoxiangzhengqi	Shufengjiedu	0.63
Paracetamol	Ibuprofen	0.87	Dequalinium chloride	Lianhuaqingwen	0.00	Huoxiangzhengqi	Lianhuaqingwen	1.00
Paracetamol	Dequalinium chloride	0.18	Dequalinium chloride	Liushenwan	0.73	Huoxiangzhengqi	Liushenwan	0.98
Paracetamol	Loratadine	0.81	Loratadine	Aspirin	0.56	Ambroxol	Acetylcysteine	0.01
Paracetamol	Aspirin	0.83	Loratadine	Qingfeipaidu	0.72	Ambroxol	Cetirizine	0.53
Paracetamol	Qingfeipaidu	0.90	Loratadine	Xuanfeibaidu	0.98	Ambroxol	Shufengjiedu	0.00
Paracetamol	Xuanfeibaidu	0.17	Loratadine	Xylometazoline	0.69	Ambroxol	Lianhuaqingwen	0.04
Paracetamol	Xylometazoline	0.27	Loratadine	Huoxiangzhengqi	0.72	Ambroxol	Liushenwan	0.01
Paracetamol	Huoxiangzhengqi	0.97	Loratadine	Ambroxol	0.41	Acetylcysteine	Cetirizine	0.99
Paracetamol	Ambroxol	0.91	Loratadine	Acetylcysteine	0.97	Acetylcysteine	Shufengjiedu	1.00
Paracetamol	Acetylcysteine	0.21	Loratadine	Cetirizine	0.99	Acetylcysteine	Lianhuaqingwen	1.00
Paracetamol	Cetirizine	0.32	Loratadine	Shufengjiedu	0.34	Acetylcysteine	Liushenwan	0.00
Paracetamol	Shufengjiedu	0.21	Loratadine	Lianhuaqingwen	0.71	Cetirizine	Shufengjiedu	0.71
Paracetamol	Lianhuaqingwen	0.92	Loratadine	Liushenwan	0.00	Cetirizine	Lianhuaqingwen	0.00
Paracetamol	Liushenwan	0.94	Aspirin	Qingfeipaidu	0.69	Cetirizine	Liushenwan	0.00
Qingyandiwan	Ibuprofen	0.01	Aspirin	Xuanfeibaidu	0.42	Shufengjiedu	Lianhuaqingwen	0.96
Qingyandiwan	Dequalinium chloride	0.94	Aspirin	Xylometazoline	0.96	Shufengjiedu	Liushenwan	0.08
Qingyandiwan	Loratadine	0.14	Aspirin	Huoxiangzhengqi	0.01	Lianhuaqingwen	Liushenwan	0.00

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