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

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Drug-drug interactions (DDIs) have significant impacts on patient health. In COVID-19, it is particularly important to be aware of DDIs due to the rapid development of new treatments and vaccines, as well as the widespread use of over-the-counter (OTC) drugs. Additionally, people who have COVID-19 may also be taking medications for comorbid conditions, increasing the potential for DDIs. Beyond the COVID-19 pandemic, the issue of drug interactions is further exacerbated by the aging population.

The "Ten Guidelines" announced by the National Health Commission of China on 7 December 2022 marks the next phase of China's fight against COVID-19 [1]. With relaxed restrictions, a surge of new infections is expected. Despite efforts to improve the public health system, hospitals are still crowded and resources are scarce [2]. Crowded hospitals are becoming a problem in multiple cities. As a result, also as prudently recommended by the health authorities, most infected Chinese, likely in hundreds of millions in this current wave of infection [3], will be enduring the entire infection and recovery phases at home as families, while making their own decisions with OTC drugs. This problem is particularly concerned in a large group of Chinese people, who use traditional Chinese medicine (TCM) products together with common OTC drugs like ibuprofen and paracetamol, without seeking medical consultation properly [4]. Our understanding of DDIs between TCM and prescription drugs (such as anti-COVID-19 drugs) is gradually expanding; however, knowledge about DDIs between TCM and OTC drugs remains limited [5]. The National Health Commission of China published guidelines for 20 OTC drugs for COVID-19 covering 12 Western medicines and 8 TCMs [6]. Despite various messaging efforts from health authorities, many patients are bound to take multiple drugs to treat the varied manifested symptoms of COVID-19 infections. The severity of such elevated DDI risk is largely unknown, particularly given the complicated and unidentified chemical composition of TCM drugs [7].

The topological relationship between two most commonly used drugs, ibuprofen (a nonsteroidal anti-inflammatory Western drug) and Lianhuaqingwen (a TCM drug composed of 13 Chinese herbal medicine) in the human body's protein-protein-interaction (PPI) network (Fig. 1) were examined as an example of the interactions. We found: (a) extensive direct PPIs between their protein targets; (b) Lianhuaqingwen has more protein targets in the human body than ibuprofen; (c) extensive

PPIs among Lianhuaqingwen's protein targets, while fewer among ibuprofen's. Although the topological relationship between the protein targets of these drugs suggesting a potentially high risk, there is no confirmed DDI between these drugs in the literature [7]. Please refer to the supplementary materials for a deep learning model [8] evaluating the DDI risk among all recommended drugs, as well as the pharmacological class of recommended OTC drugs.

The potentially harmful drug interactions between TCM and OTC drugs, and within OTCs can vary depending on the specific combination of medicines, including interfering with drug absorption, increasing risk of bleeding, liver damage, high blood pressure, and so on [4]. Our findings on the potential risk of DDIs within OTC drugs, particularly in the context of the COVID-19 pandemic, call for immediate action. Raising public awareness of the potential risks associated with taking multiple OTC drugs is critical. Additionally, further investigation into high-risk drug pairs that have not been clinically verified is necessary to ensure patient safety. Due to the requirement for lengthy clinical drug interaction studies by drug regulators to confirm DDIs, individuals are often left vulnerable to potential DDIs during emerging infectious disease outbreaks, when rapid identification and treatment are necessary. To address this issue, it is crucial to leverage existing knowledge of pharmacokinetics and pharmacodynamics, and to utilize computational tools, such as deep learning and network science models, to provide data-driven warnings to patients and pharmacists. This can aid in regulating the use of OTC drugs to minimize the risk of DDIs during the pandemic.

DDIs pose a risk to patients of all ages and health conditions, not just those with COVID-19. TCM and other herbal supplements have gained popularity in the Western Pacific region, leading to the potential for interactions with Western medicines. TCM has been deeply rooted in many East Asian cultures for centuries, with the use of herbs and herbal formulas often perceived as a safer and more natural alternative to Western medicine. As a result, many patients use TCM in conjunction with Western medicines, often without informing their primary physicians. This lack of communication can lead to potential DDIs and other health risks, highlighting the importance of patient education and communication with healthcare providers. The aging population and the use of multiple medications for comorbid conditions, further

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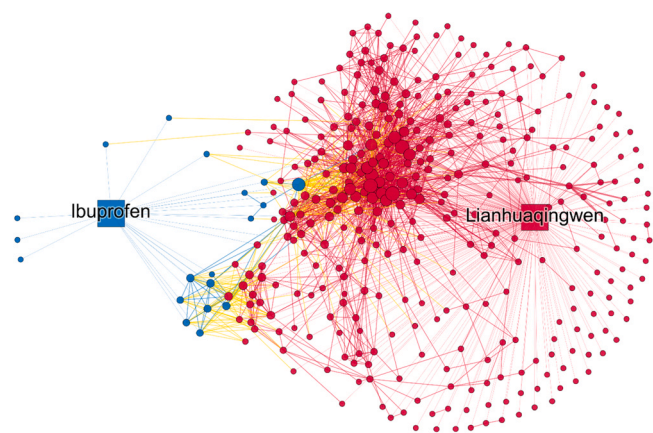


Fig. 1. The visualization of the protein-protein interactions among the protein targets of ibuprofen and Lianhuaqingwen in the human body. The big blue square is ibuprofen. The big red square is Lianhuaqingwen. The blue circle nodes indicate protein targeted by ibuprofen. The red circle nodes indicate protein targeted by Lianhuaqingwen. The size of a circle node is proportional to its degree. The blue edges indicate the protein interactions between proteins targeted by ibuprofen. The red edges indicate the protein interactions between proteins targeted by Lianhuaqingwen. The yellow edges indicate the protein interactions between ibuprofen targets and Lianhuaqingwen targets.

underscores the urgency of addressing this issue. It is crucial for healthcare providers to inquire about patients' use of TCM and other supplements when prescribing Western medications. Policymakers must recognize the potential risk of DDIs and take action to regulate the co-use of Western and TCM drugs for various conditions. Additionally, patients should be informed of the potential risks of DDIs and advised to inform their healthcare providers of any TCM or other supplements they are taking. Highlighting the importance of DDIs can improve patient outcomes and promote better health for all. By working together, healthcare providers, policymakers, and patients can take proactive steps to reduce the risk of DDIs and ensure that medications are used safely and effectively.

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CRedit authorship contribution statement

Qingpeng Zhang, Jiannan Yang contributed to the conceptualization, the writing, reviewing and the approval of the final version of the paper. **Daniel Dajun Zeng, Yibin Feng and Ian C.K. Wong** contributed to the writing, reviewing and the approval of the final version of the paper.

Declaration of Competing Interest

We have no conflicts of interest to disclose.

Data availability

Please refer to <https://github.com/JasonJYang/GCN-DDI-TCM> for the data, code and results, and <https://drugcompassdemo.compasshealth.ai/> for an interactive visualization platform.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.phrs.2023.106903](https://doi.org/10.1016/j.phrs.2023.106903).

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