Drug repurposing for COVID-19: could vitamin C combined with glycyrrhizic acid be at play by the findings of Li et al.’s database-based network pharmacology analysis?

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Abstract

The outbreak and pandemic of SARS-CoV-2 in 2019 has caused a severe public health burden and will challenge global health for the future. The discovery and mechanistic investigation of drugs against Coronavirus disease 2019 (COVID-19) is in deadly demand. The paper published by Li and colleagues proposed the hypothesis that vitamin C combined with glycyrrhizic acid in treating COVID-19 and its mechanistic investigation was performed by a database-based network pharmacology. In this letter, we present critical comments on the limitations and insufficiencies involved, from both the perspective of network pharmacology and current evidence on COVID-19.

Key words: COVID-19; vitamin C; glycyrrhizic acid; network pharmacology

As of 2 October 2020, coronavirus disease 2019 (COVID-19) has affected more than 34 million people globally, which is straining worldwide healthcare capacity. Currently, although many studies have been carried out on the epidemiology, clinical characteristics, diagnosis, treatment and prevention of COVID-19, there is still no specific antiviral drug for this deadly disease [1, 2]. On July 20, the results of a phase II clinical study of a recombinant adenovirus type-5 vectored COVID-19 vaccine were published, which showed this vaccine was safe and could induce an immune response in humans [3]. Although such encouraging progress has been made, it will be a long time before vaccine can be mass-produced and widely used. Thus, people are seeking ways in which to potentially protect themselves from this virus or to alleviate its conditions once caught. One such means that is being touted online and in the media is intravenous vitamin C (VC) [4]. We congratulate Li and colleagues for their recent study on VC combined with glycyrrhizic acid (GA) in treating COVID-19 based on network pharmacology analysis.
In this routine network pharmacology work, they first obtained the target proteins of VC and GA and the related target genes of COVID-19 by database strategy, then GO biological processes and KEGG enrichment analysis were performed on the overlapping targets of VC and GA with COVID-19, respectively, and finally a drug-target-GO-KEGG-disease relationship network was constructed to dissect the mechanism of VC combined with GA on COVID-19. However, in the section of targets screening, many databases such as TCMSP, SuperPred, ChemMapper, Batman-TCM were all updated earlier than December 2016. It is questionable whether overly lagging knowledge can facilitate mechanistic investigations of VC, GA and their combination against COVID-19 [6]. Of note, keywords such as ‘SARS-CoV-2 pathogenic targets’ and ‘COVID-19 related gene’ were proposed in Li’s paper, but there is still no clear ‘SARS-CoV-2’ or ‘COVID-19’ targets according to the current evidence. Expectedly, no exact matches of ‘COVID-19 related gene’ were acquired from OMIM and GeneCards as described in the paper, whereas several databases containing COVID-19 information have been reported, such as TCMAntiCOVID-19V1.0 (http://tcmaclow.bbtcmi.com/) and D3Targets-2019-nCoV (https://www.d3pharma.com/D3Targets-2019-nCoV/index.php). Moreover, the databases involved in Li’s study, including TCMSP, SuperPred, SwissTargetPrediction, ChemMapper, BATMAN TCM and SuperPred webserver, are mainly based on computational algorithm to predict the drug-target interactions. For example, SwissTargetPrediction could only achieve at least one correct human target in the top 15 predictions for >70% of external compounds [7]. For this reason, the interactions between drugs and targets obtained by database strategy should be validated and quantified at least by molecular docking and molecular dynamics simulation [8]. In the section of GO biological process and KEGG pathway enrichment, it is far from adequate to only rely on gene count and gene ratio enriched in the corresponding items (GO biological process or KEGG pathway) to determine the top biological processes and KEGG pathways. For network pharmacology, it is crucially important to identify the core targets, biological processes and pathways through network topology analysis in case of the drug-target-GO-KEGG-disease network has been constructed.

Since the authors have proposed the hypothesis that VC combined with GA in treating COVID-19, it is of great significance to consider them as a whole, rather than focusing on the overlapping targets of VC and GA against COVID-19, respectively. Specifically, the analysis should be based on the overlapping targets (45 in total) between the combination (VC + GA) and COVID-19, rather than the overlapping targets (17 in total) of VC, GA and COVID-19 mentioned in Li’s paper. Meanwhile, the dosage and ratio are crucially important parts of a drug combination to exert its efficacy, but there is a lack of such information in Li’s paper. Although network pharmacology is not responsible for the optimal dosage, given the current development of network pharmacology techniques and the background of ‘big data’, the ratio should be taken into account at least based on many valuable clinical data of VC and GA [9, 10]. Theoretically, a drug combination may produce synergistic, additive or antagonistic effects if the combinational effect is greater than, equal to or less than the sum of each individual drug [11]. However, in Li’s paper, there is no clear conclusion on the combination of VC and GA, that is, whether it has synergistic, additive, or antagonistic effect still remains unknown. And, last but not least, it will be crucially significant for the mechanism investigation of VC and GA against COVID-19 by network pharmacology analysis coupled with experimental validation.

VC is best known for its antioxidant properties, being able to scavenge damaging reactive oxygen species, thus protecting the body’s cells and tissues from oxidative damage and dysfunction [4]. GA is a major bioactive ingredient extracted from Rhizoma Glycyrrhizae, which has evident pharmacological properties on detoxifying, cough-relieving, anti-inflammatory, anti-tumor, antibacterial and potential antiviral capacity [5]. While acute respiratory distress syndrome (ARDS) is a key factor of fatality in COVID-19, it is characterized by significantly increased oxidative stress due to the rapid release of free radicals and cytokines, which could lead to cellular injury, organ failure and death [12]. Hence, early use of large dose antioxidants coupled with antiviral agents, such as VC and GA, seems to be an effective treatment for COVID-19 patients. A recently published randomized controlled trial (RCT) carried out in the USA in 167 patients with sepsis related ARDS indicated that administration of ~15 g/day of intravenous VC for 4 days may decrease mortality [13]. Furthermore, one of the major causes for concern with COVID-19 is the relatively high proportion of cases requiring intensive care unit (ICU) treatment, and a meta-analysis of 12 trials with 1766 patients in ICU found that VC shortened ICU stay by 8% [14]. However, the same RCT conducted on patients with sepsis and ARDS reported no difference in the primary outcome of organ failure scores and inflammation biomarkers which requires us to determine the effects of VC more dialectically and objectively [13]. Moreover, intravenous high-dose VC was recommended against COVID-19 and yet intravenous VC administered in gram doses can cause serious side effects in some patients (haemochromatosis, G-6-PD deficiency, renal dysfunction, renal stones or oxaluria, etc.) [15]. So, it is essential to evaluate the dosage and ratio of VC-GA before its clinical application for COVID-19.

Collectively, the discovery and mechanistic investigation of new drug combination against COVID-19 should be based on evidence rather than relying solely on a database-based network pharmacology, and not dominated by mainstream media and subjective assumptions, even in such a crisis.

Key Points

- We presented here critical comments on the paper published in Briefings in Bioinformatics on the combination of vitamin C and glycyrrhizic acid against COVID-19 by a database-based network pharmacology analysis.
- Due to the lag of database update and the unclear targets of COVID-19, the reference significance of Li’s study is limited.
- The hypothesis of vitamin C-glycyrrhizic acid as a potential option for treating COVID-19 without empirical data supports and definitive references may lead to the false appearance of excessive efficacy and the safety hazard of the drug.
- It is essential to evaluate the dosage and ratio of vitamin C-glycyrrhizic acid before its clinical application for COVID-19.

Author contributions

Yu-Xi Huang and Wen-Xiao Wang collected and analyzed the data. Shi-Jun Yue and Yu-Ping Tang directed the research. Yu-Xi Huang, Wen-Xiao Wang and Shi-Jun Yue wrote the
manuscript. Shi-Jun Yue and Yu-Ping Tang reviewed and revised the manuscript.

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