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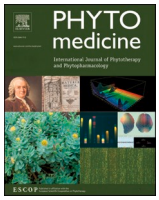

Original Article

Glycyrrhetinic acid: A potential drug for the treatment of COVID-19 cytokine storm

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ABSTRACT

Background: The cytokine storm (CS) triggered by coronavirus disease 2019 (COVID-19) has caused serious harm to health of humanity and huge economic burden to the world, and there is a lack of effective methods to treat this complication.
Purpose: In this research, we used network pharmacology and molecular docking to reveal the interaction mechanism in the glycyrrhetinic acid (GA) for the treatment of CS, and validated the effect of GA intervention CS by experiments.
Study design: First, we screened corresponding target of GA and CS from online databases, and obtained the action target genes through the Venn diagram. Then, protein-protein interaction (PPI) network, Gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment of the action target genes were acquired by R language to predict its mechanism. Next, molecular docking was performed on core targets. Finally, experiments in which GA intervened in lipopolysaccharide (LPS)-induced CS were implemented.
Results: 84 action target genes were obtained from online database. The PPI network of target genes showed that TNF, IL6, MAPK3, PTGS2, ESR1 and PPARG were considered as the core genes. The results of GO and KEGG showed that action target genes were closely related to inflammatory and immune related signaling pathways, such as TNF signaling pathway, IL-17 signaling pathway, Human cytomegalovirus infection, PPAR signaling pathway and so on. Molecule docking results prompted that GA had fine affinity with IL6 and TNF proteins. Finally, *in vivo* and *in vitro* experimental results showed that GA could significantly inhibit LPS-induced CS.
Conclusion: GA has a potential inhibitory effect on CS, which is worthy of further exploration.

Introduction

COVID-19 is a huge catastrophe that has infected more than 400 million people and killed more than 6 million by April 2022, and the number of infections and deaths is increasing daily (https://covid19.who.int/). Many of those who died from COVID-19 induced hyper-inflammation characteristic of cytokine storm (CS) and related acute respiratory distress syndrome (ARDS) (Cron et al., 2021). CS is an out-of-control systemic inflammation disease induced by an overload of cytokines that led to multi-organ failure and even death (Behrens and Koretzky, 2017; Yongzhi, 2021). It is considered to be the main cause of severe COVID-19 patients. In general, the diseases are progressively aggravated as cytokine levels increase in COVID-19 patients (Pedersen and Ho, 2020). For example, patients who required admission to the ICU have significantly elevated levels of IL-6, TNF-α, IL-10, IL-2, etc. It is suggested the significance of CS in the pathogenesis and prognosis of

Abbreviations: CS, cytokine storm; COVID-19, coronavirus disease 2019; GA, glycyrrhetinic acid; PPI, protein-protein interaction network; GO, gene ontology; KEGG, kyoto encyclopedia of genes and genomes; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; GLR, glycyrrhizic acid; MF, molecular function; BP, biological process; CC, cellular composition; LPS, lipopolysaccharides; DMSO, dimethyl sulphoxide; BALF, bronchoalveolar lavage fluid; DEX, dexamethasone sodium phosphate injection.

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