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Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by the previously unknown pathogen, severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) is now a global pandemic. There are no vaccines or specific treatments against this new virus; therefore, there is an urgent need to advance novel therapeutic interventions for COVID-19. Glycyrrhizin is a triterpene saponin with various biological functions and pharmacological effects. This brief article discusses the therapeutic potential of glycyrrhizin for the treatment of COVID-19 from the perspective of its pharmacological action, including binding angiotensin-converting enzyme II (ACE2), downregulating proinflammatory cytokines, inhibiting the accumulation of intracellular reactive oxygen species (ROS), inhibiting thrombin, inhibiting the hyperproduction of airway exudates, and inducing endogenous interferon.

In December 2019, an outbreak of pneumonia caused by a previously unknown pathogen gained tremendous attention. The pathogen, a novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread worldwide within a few weeks. The World Health Organization (WHO) has so far reported more than 1.8 million confirmed cases worldwide, including more than 100 000 deaths. There is no specific treatment against the new virus; therefore, effective agents to combat the resulting disease, coronavirus disease 2019 (COVID-19), are urgently needed.

The SARS-CoV-2 is considered to share 79.5% of the genetic sequence of SARS-CoV and to have the same cell entry receptor, angiotensin-converting enzyme II (ACE2) [1]. In addition, infection caused by the SARS-CoV-2 shares many clinical similarities with infection caused by SARS-CoV [2]. Given the similarities between SARS-CoV and SARS-CoV-2, we can take some cues from the research and clinical experience of SARS-CoV to manage SARS-CoV-2-infected pneumonia (COVID-19). Research on SARS-CoV has identified a variety of agents with the potential to treat SARS-CoV infection. Glycyrrhizin is a triterpene saponin with various biological functions and pharmacological effects and is one of the most promising candidates as it was found to be active against SARS-CoV in vitro [3]. Moreover, modification of glycyrrhizin may create novel anti-SARS-CoV drugs with increased activity [4]. Considering the experience and lessons of the fight against SARS, glycyrrhizin may be a promising candidate for treatment of COVID-19 and deserves further evaluation.

Glycyrrhizin has been shown to inhibit viral adsorption and penetration, and was most effective when administered both during and after the viral adsorption period [5]. There is also considerable evidence to show that glycyrrhizin can interfere with the replication and/or cytopathogenic effect of many respiratory viruses [3,6]. This brief article discusses the therapeutic potential of glycyrrhizin for the treatment of COVID-19 from the perspective of its pharmacological action.

Recent research indicates a strong interaction of SARS-CoV-2 with human ACE2 [7,8]. Moreover, the results from Letko et al. showed that the SARS-CoV-2 receptor-binding domain could enter cells expressing human host cell ACE2, not any of the other receptors, further confirming that human ACE2 is the receptor for the recently emerging SARS-CoV-2 [9]. As the host cell receptor is critical for virus entry, targeting ACE2 is a promising potential strategy for preventing SARS-CoV-2 infection and, more valuably, inhibiting the virus from diffusing out of the infected cell and attaching to and entering new permissive target cells, thus arresting late deterioration. Glycyrrhizin has recently been shown to have the potential to bind to ACE2 [10]. Although this research was performed in silico using molecular docking, and the in vitro demonstration of an interaction remains to be confirmed, glycyrrhizin might still be considered as a potential treatment for COVID-19 as it has an antiviral effect on SARS-CoV (ACE2 was also a functional receptor for the SARS-CoV [11]).

Cytokine storm is mediated by overproduction of proinflammatory cytokines, including interferons (IFNs), tumor necrosis

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factors (TNFs), interleukins (ILs), and chemokines, and can exacerbate pathological damage in hosts [12]. The cytokine storm observed in a large population of critically ill patients with COVID-19 was associated with disease severity [13]. Some patients who suffered from cytokine storm progressed rapidly to acute respiratory distress syndrome and septic shock, which was eventually followed by multiple organ failure [14]. Therefore, early identification and timely intervention for patients with cytokine storm is of crucial importance. During the SARS outbreak in 2003, glucocorticoids were widely used in patients with cytokine storm. Corticosteroids exert an anti-inflammatory effect and are indicated for the treatment of respiratory distress caused by cytokine storm; however, they also exert an immunosuppressor effect and limit viral clearance by the immune system [5]. Furthermore, long-term use or large doses of glucocorticoids are restricted because of glucocorticoid-induced osteonecrosis of the femoral head. Whether corticosteroids should be used in COVID-19 is therefore uncertain. Glycyrrhizin has cytokine-modulating activity, it is not an immunosuppressant like glucocorticoids, and may even enhance the immune response [15]. Therefore, glycyrrhizin is expected to be used in the early stages of disease and can be administrated for a longer time, with fewer side effects; this approach holds promise for preventing or attenuating excessive cytokine storms in patients with COVID-19.

As reactive oxygen species (ROS) have a crucial role in inflammatory response, antioxidants may also be effective for the treatment of cytokine storm induced by infection [12]. Glycyrrhizin can inhibit the accumulation of intracellular ROS caused by virus infection [6,16]. Inhibition of ROS formation by glycyrrhizin can also reduce the activation of nuclear factor kappa beta (NFkB), c-Jun N-terminal kinase (JNK), p38, and redox-sensitive signaling events that are known to be relevant for virus replication [6], thereby suppressing virus replication. In addition, a sustained inflammatory or cytokine storm response caused by SARS-CoV-2 can result in activation of coagulation and complement cascades [2], which may contribute to multiple organ failure. Data showed that glycyrrhizin is a selective inhibitor of thrombin [17,18]. These integrated results indicate that glycyrrhizin has potential therapeutic benefits for COVID-19 through multisite mechanisms.

Pathological findings of COVID-19 showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates [19]. Hypoxia commonly occurs when alveolar function is impaired and the airway is simultaneously blocked by mucus. Thus, inhibiting the hyperproduction of airway exudates is an effective approach to prevent severe hypoxia. Interestingly, glycyrrhizin also has an inhibitory effect on airway mucus hyperproduction through the inhibition of MUC5AC gene transcription [20]. Therefore, glycyrrhizin may alleviate anoxia and improve clinical symptoms in COVID-19 patients.

Moreover, glycyrrhizin has been reported to induce endogenous interferon [21]. Interferon is recommended in all seven versions of the *Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus* issued by the *National Health Commission of China*, probably because of the recent experience of clinical practice on COVID-19 and previous benefits in treatment of severe Middle East respiratory syndrome (MERS)-CoV infection [22]. As interferon is a broad-spectrum antiviral, it would limit virus spread by inhibiting replication of both DNA and RNA viruses at different stages of their replicative cycles and by activating immune cell populations to clear virus infections [23]. Accordingly, glycyrrhizin may also play an indirect role in treatment of COVID-19. In the absence of a targeted vaccine or a pathogen-specific antiviral, many drugs with antiviral potential have been investigated recently for the treatment of COVID-19. Drug-induced liver injury has become a serious health problem. Glycyrrhizin, with its known liver-protection effects, may play an auxiliary role in COVID-19 treatment.

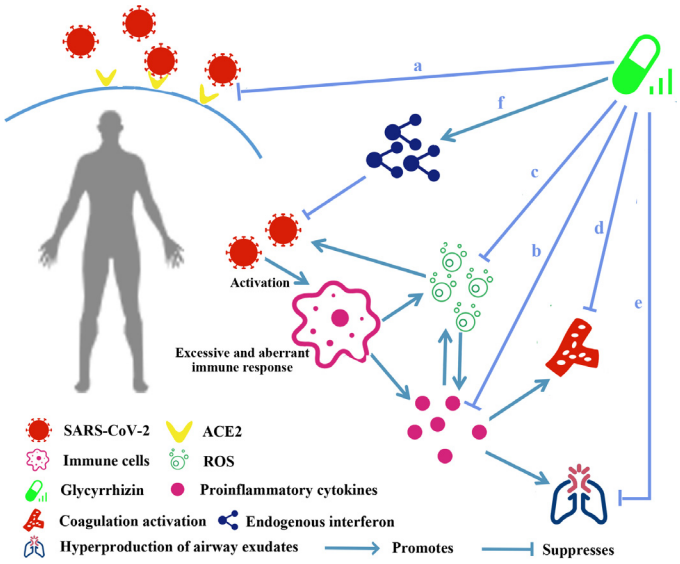

Fig. 1. SARS-CoV-2 invades human alveolar epithelial cells via the ACE2 receptor and causes exaggerated and aberrant host immune responses. The exaggerated immune responses lead to the overproduction of proinflammatory cytokines and reactive oxygen species (ROS), which might cause functional disability and even death. Exaggerated inflammation could also activate coagulation and spark a surge of airway exudates that contribute to multiple organ failure and anoxia state in COVID-19 patients. Glycyrrhizin might possess therapeutic benefits for COVID-19 with multisite mechanisms, including: a) Binding ACE2 to prevent SARS-CoV-2 infection. b) Downregulating proinflammatory cytokines. c) Inhibiting the accumulation of intracellular ROS. d) Inhibiting thrombin. e) Inhibiting the hyperproduction of airway exudates. f) Inducing endogenous interferon to combat the SARS-CoV-2.

There is currently no specific treatment available for the new virus. Thus, identifying novel and effective treatments is imperative and would be of great benefit to patients. Although numerous clinical trials are underway worldwide to find effective drugs for COVID-19 treatment, no drug has been announced to be effective so far. Glycyrrhizin is valued for its various pharmacological effects and may emerge as a promising agent for the treatment of COVID-19 (Fig. 1). More importantly, some derivatives of glycyrrhizin that have a much higher antiviral activity than glycyrrhizin itself [4] might also be a good option. However, there are some crucial points that should be considered. Close attention should be given to the side effects of glycyrrhizin, particularly in elderly patients with heart disease and hypertension. In addition, the biological function of glycyrrhizin is drawn from in vitro findings and animal experiments and may not correspond with clinical efficacy in humans; therefore, the exact clinical curative effect and the optimal dose and course of treatment must be further assessed.

Declarations

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