

Glycyrrhizin in licorice root neutralizes SARS-CoV-2 in vitro by inhibiting the main protease Mpro

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COVID-19 disease, caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a range of symptoms from mild to severe respiratory illness. Unfortunately, even pre-symptomatic patients or those with very mild symptoms are infectious and can infect other people.

The need of the hour is effective and well-tolerated therapeutic options to treat patients with severe COVID-19. Besides compounds such as remdesivir have been approved or authorized for emergency use to treat COVID-19, traditional herbal medicines are considered promising candidates for the complementary treatment of viral diseases and recently suggested for the treatment of COVID-19.

Analyzing the neutralizing activity of licorice root extract against SARS-CoV-2 in vitro

In a recent [bioRxiv](#)* preprint paper, researchers from Germany analyzed aqueous licorice root extract for its neutralizing activity against SARS-CoV-2 in vitro. They identified glycyrrhizin, the primary active ingredient in the root, and revealed the underlying mechanism of viral neutralization.

The licorice roots were dried and brewed, and the resulting fluid was sterile filtered to obtain an aqueous extract of the root. The neutralization capacity of the extract was determined in cell culture using endpoint dilution. Cytotoxicity was determined at 4 time points - 5 minutes, 12 hours, 24 hours and 48 hours - using the "Orangu cell counting solution", which is an assay that uses NAD(P)H concentration and dehydrogenase enzyme activity to detect cell vitality.



Licorice root extract neutralized SARS-CoV-2 even at a subtoxic concentration

The licorice root extract exhibited neutralizing effects even at a subtoxic concentration of 2 mg/ml, which is lower than the typical consuming dilution. For example, in tea, it is 12.5 mg/ml. Although this shows that licorice root tea may be a candidate for complementary use as an antiviral, it is crucial that the active compound is identified and characterized for its potential consideration in clinical applications.

"Complete virus neutralization was achieved at subtoxic concentrations of 0.5 mg/ml under pre- and 1 mg/ml under post-entry conditions."

Glycyrrhizic acid - antiviral active ingredient in licorice root

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Glycyrrhizic acid is a triterpene saponin that is found in high concentrations in the root of the *Glycyrrhiza glabra* plant. It was found to be the active antiviral ingredient in licorice root and it exhibits antiviral activity against many viruses, including herpes simplex viruses, the human immunodeficiency virus (HIV), and human and animal coronaviruses.

An in-silico simulation study suggested antiviral activity of glycyrrhizin against SARS-CoV-2, but this hypothesis had not been experimentally proved. Based on

the results obtained in the aqueous licorice root extract, the researchers investigated the neutralizing activity of glycyrrhizic acid against a SARS-CoV-2 isolate and subsequently examined the mechanism of neutralization.

“Glycyrrhizin was clinically evaluated in the context of a clinical trial and described to be a safe and well-tolerated compound”

Glycyrrhizin inhibits SARS-CoV-2 main protease

The human transmembrane serine protease (TMPRSS2) has been shown to cleave the SARS-CoV-2 [spike protein S](#), thus facilitating the entry of the virus into the host cell. However, the researchers found only a tiny difference in the antiviral activity of glycyrrhizin between pre- and post-entry conditions. So they concluded that glycyrrhizin neutralizes the virus by a mechanism that is different from inhibition of TMPRSS2 and hence focused on the SARS-CoV-2 main protease (Mpro) as its potential target.

“Taken together, we demonstrated that glycyrrhizin, the primary active ingredient of the licorice root, potently neutralizes SARS-CoV-2 by inhibiting the viral main protease.”

Mpro is responsible for the processing of viral polyproteins translated from the viral RNA and hence essential for virus replication. In their experiments, researchers found that glycyrrhizin fully inhibited Mpro activity at a concentration of 2000 μM (1.6 mg/ml) and reduced Mpro activity by 70.3% at a concentration of 30 μM (0.024 mg/ml). Thus, they concluded that glycyrrhizin effectively neutralizes SARS-CoV-2 by inhibiting the viral main protease Mpro. These findings highlight glycyrrhizin as a promising antiviral compound that should be further studied for use in the treatment of COVID-19.

“The potent antiviral activity as well as anti-inflammatory properties highlight glycyrrhizin as an excellent candidate for further clinical investigations in COVID-19 treatment.”

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Journal reference:

- Glycyrrhizin effectively neutralizes SARS-CoV-2 in vitro by inhibiting the viral main protease L. van de Sand, M. Bormann, M. Alt, L. Schipper, C.S. Heilingloh, D. Todt, U. Dittmer, C. Elsner, O. Witzke, A. Krawczyk *bioRxiv* 2020.12.18.423104; doi: <https://doi.org/10.1101/2020.12.18.423104>, <https://www.biorxiv.org/content/10.1101/2020.12.18.423104v1>

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