

# Licorice and its applications for SARS-CoV-2

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## Abstract

Licorice is a common Chinese herbal medicine in China. Glycyrrhizic acid (C<sub>42</sub>H<sub>62</sub>O<sub>16</sub>), and glucoside are the major active chemical ingredients that possess antioxidant, antiviral, anti-infective, and anti-inflammatory properties. It can either cure (e.g. SARS-CoV-2) or cause diseases (e.g. hypertension or heart attack), so care is needed in the dosage of licorice. Some library search engines were used such as SCI/SCIE, PubMed, and Scopus. In this mini-review, the keywords searched include “licorice”, “traditional Chinese medicine + licorice”, “SARS-CoV-2”, “licorice + SARS-CoV-2” etc. in the last thirty years. The author discusses the background, usage, risk of licorice, the research progress on its antiviral activity as well as some Traditional Chinese Medicine (TCM) formulations for the prevention and treatment of COVID-19.

## Introduction

Licorice is a flowering plant and has been used as Chinese herbal medicine in China for a long time. It belongs to the family of *Leguminosae*, which is derived from *Glycyrrhiza glabra*. The major active chemical ingredients consist of glycyrrhizic acid (C<sub>42</sub>H<sub>62</sub>O<sub>16</sub>), and glucoside (Figure 1). Growing evidence has shown that the root of licorice presents different properties, such as antioxidant, antiviral, anti-infective, and anti-inflammatory properties. According to the Traditional Chinese Medicine (TCM) theory, licorice has the function to tonify and nourish the “qi”, invig-

orate the spleen and harmonize the stomach, clear heat, detoxify, reduce phlegm, relieve cough, and alleviate pain.<sup>1</sup> It also helps to moderate other herbs in the TCM formulation.

## Risk of Licorice

Licorice is also used as a flavoring in candies called “Black licorice”. However, excess consumption of glycyrrhizic may result in adverse effects, e.g. hypertension crisis, muscle breakdown, and heart disease. The safety level of glycyrrhizin is considered as 0.2 mg/kg/day.<sup>2</sup>

Ottenbacher *et al.* identified large quantities of glycyrrhizic acid-induced hypertension. Glycyrrhizic acid affects the level of sodium and potassium causing edema, hypokalemia, metabolic alkalosis, and low plasma renin activity. The type 2 isoenzyme of 11  $\beta$ -hydroxysteroid dehydrogenases (11 $\beta$ -HSD) is suppressed leading to cortisol inactivation and mineralocorticoid excess (AME) in the renal collecting tubules.<sup>3</sup> Deutch *et al.* explained the tribasic glycyrrhizin might have existed in calcium and potassium salts forms. 3 $\beta$ -monoglucuronyl-18 $\beta$ -glycyrrhetic acid (3MGA) and an aglycone 18 $\beta$ -glycyrrhetic acid are hydrolyzed from glycyrrhizin after oral ingestion. This promoted potassium levels in the body to fall, causing abnormal heart rhythms and congestive heart failure.<sup>4</sup> Srivatsa *et al.* discovered the active component of glycyrrhizin as a thrombin inhibitor and metabolized warfarin through the suppression of a P450 system. Its prolonged fibrinogen clotting times, the anti-thrombotic activity influenced the function of blood anti-coagulation either in cardiovascular or renal systems.<sup>5</sup>

## Case study of licorice

On the 24<sup>th</sup> of September in 2020, a 54-year-old man died who ate several packages of licorice-flavored candy daily. The glycyrrhizic acid of black licorice resulted in uncontrolled cortisol levels and caused some diseases such as hypertension, hypokalemia, metabolic alkalosis, fatal arrhythmias, and renal failure.<sup>6</sup> Given this phenomenon, the Food and Drug Administration (FDA) issued in early 2017 who are 40 years of age or above cannot intake a maximum of two ounces per day of black licorice, otherwise, it may risk of irregular heart rhythm or arrhythmia.<sup>7</sup>

## Research progress of licorice on antiviral activity

Glycyrrhizic acid is one of the bioactive components in licorice that possess an antiviral function. In early 1979, Pompei *et al.* reported glycyrrhizic acid could suppress the growth and cytopathology of four viruses including vaccinia, herpes simplex, newcastle disease, and vesicular stomatitis.<sup>8</sup> Badam *et al.* discovered the concentration of licorice and ammonium salt of glycyrrhizic acid are only required 1000 micrograms/mL which inhib-

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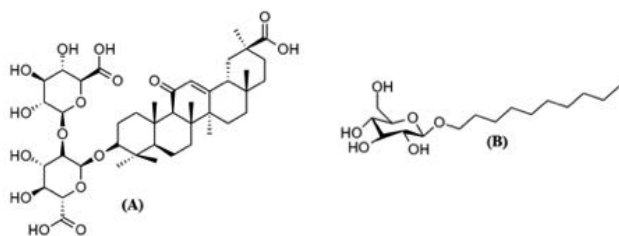
ited the formation of plaque in the Japanese Encephalitis Virus (JEV). This was non-toxic to the kidney.<sup>9</sup> Lin *et al.* also identified glycyrrhizic acid could inhibit the infection of Epstein-Barr Virus (EBV) by interfering with its virus self-replication cycle in the early stage. The concentration of glycyrrhizic acid was 7.5 times more active against EBV. It was increasing the cytotoxicity of EBV resulting in an enhanced therapeutic index.<sup>10</sup> Another research from Bentz *et al.* found that glycyrrhizic acid was not affected inducing reactivation of the virus, but it could reduce the ability of a virus self-replication to infect additional cells for the treatment of EBV-associated lymphoid malignancies.<sup>11</sup> Ashfaq *et al.* reported glycyrrhizic inhibited Hepatitis C Virus (HCV) and HCV core gene expression or function in a dose-dependent manner causing synergistic effect with interferon.<sup>12</sup> Michaelis *et al.* reported glycyrrhizin suppresses with H5N1 replication and H5N1-induced pro-inflammatory gene expression. It inhibited the formation of Reactive Oxygen Species (ROS) in H5N1 and reduced the activation of NFκB, JNK, and p38 to interference with the influenza A virus replication.<sup>13</sup>

## SARS-CoV-2

SARS-CoV-2 is a beta-coronavirus with 79% genome sequence identity with SARS-CoV and 50% with MERS-CoV.<sup>14</sup> This enters into the host cell by fusion and envelope with the cell membrane or membrane fusion within the endosome after endocytosis. The virus is activated by binding the Receptor-Binding Domain (RBD) of the S protein to an Angiotensin-Converting Enzyme 2 (ACE2) receptor at the cell surface causing the infection of the respiratory tract and lung.<sup>15</sup>

## Licorice inhibits SARS-CoV-2 activity

Van de Sand *et al.* identified glycyrrhizin prevents the SARS-CoV-2 spike protein replication as its inhibiting the SARS-CoV-2 main protease M<sup>pro</sup>. Transmembrane Serine Protease (TMPRSS2) is effective to block the entry of its virus invade. The glycyrrhizin in licorice is a neutral inhibitor for the SARS-CoV-2 main protease.<sup>16</sup> Murck *et al.* discovered the effect of glycyrrhizic acid on a SARS-CoV-2 transmission, which involved the expression of type 2 Transmembrane Serine Protease (TMPRSS2) to reduce its uptake. Glycyrrhizin could reduce the severity of infection with COVID-19 include blocking the number of active sites and providing an ACE2 independent anti-inflammatory mechanism.<sup>17</sup>



**Figure 1.** Chemical structure of (A) glycyrrhizic acid (C<sub>42</sub>H<sub>62</sub>O<sub>16</sub>) and (B) glucoside.

## TCM formulations of Licorice for SARS-CoV-2

Licorice is a guiding drug in some TCM formulations for the treatment and prevention of SARS-CoV-2 including *Qingfei paidu* decoction, *Qingfei toxie fuzheng* decoction, and *Gan cao gan jiang* decoction. These treatments and preventions are the functions to store, regulate vital *qi* for strengthening an immune system in the lung and spleen to fight against SARS-CoV-2.<sup>18</sup>

## Conclusion

All of the above information demonstrates that licorice has many pharmacological properties but it must pay attention to the “dosage”, especially black licorice in western countries as a consumer product. Its active ingredient of glycyrrhizic acid either cure (*e.g.* SARS-CoV-2) or cause diseases (*e.g.* hypertension or heart attack).

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