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Licorice: A Potential Herb in Overcoming SARS-CoV-2 Infections

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Abstract

The management of the global pandemic outbreak due to the coronavirus disease (COVID-19) has been challenging with no exact dedicated treatment nor established vaccines at the beginning of the pandemic. Nonetheless, the situation seems to be better controlled with the recent COVID-19 vaccines roll-out globally as active immunisation to prevent COVID-19. The extensive usage and trials done in recent outbreak in China has shown the effectiveness of traditional Chinese Medicines (TCM) in improving the wellbeing of COVID-19 patients. Therefore, COVID-19 Prevention and Treatment guidelines has listed a number of recommended concoctions meant for COVID-19 patients. Licorice, more commonly known as Gancao in Chinese Pinyin, is known as one of the most frequently used ingredients in TCM prescriptions for treatment of epidemic diseases. Interestingly, it is deemed as food ingredient as well, where it is normally used in Western cuisines' desserts and sweets. The surprising fact that licorice appeared in the top 10 main ingredients used in TCM prescriptions in COVID-19 has drawn great attention from researchers in revealing its biological potential in overcoming this disease. To date, there are no comprehensive review on licorice and its benefits when used in COVID-19. Thus, in this current review, the possible benefits, mechanism of actions, safety and limitations of licorice were explored in hope to provide a quick reference guide for its preclinical and clinical

experimental set-up in this very critical moment of pandemic.

Keywords

licorice, COVID-19, SARS-CoV-2, *Glycyrrhizae*, anti-viral

Introduction

In accordance to the Chinese Pharmacopeia, licorice is able to replenish “Qi” (a vital energy that flows through the body to maintain one’s well=being), tonify spleen, remove heat, prevent toxicity, remove phlegm, relieve cough, spasm and pain which results in harmonizing other medicines’ effects.[1] The information and data obtained through experimental and clinical studies had shown that licorice or *Glycyrrhizae* (GR) possesses antiviral, anti-inflammatory, immunomodulatory, antimicrobial, antitussive and expectorant activities.[2,3] In addition, gastroprotective, hepatoprotective, anticonvulsant, anti-tumor, antioxidant, antidiabetic, anti-asthma, anti-allergic, antispasmodic, blood cholesterol lowering effect, increment in bile secretion, and other pharmacological effects can be elicited by licorice and its constituents.[2,3]

Novel acute respiratory infectious disease named coronavirus disease (COVID-19) patients can be classified according to the following categories; asymptomatic or presymptomatic, mild, moderate, severe or critical illness.[4] SARS-CoV-2 virus spreads mainly via respiratory droplets when infected person coughs or sneezes. Previously, the preventive measures to reduce the rate of transmission were only via physical distancing, wearing mask and hand hygiene as there are no approved treatment or vaccines to fight this pandemic. Recently, COVID-19 vaccination has began worldwide after receiving emergency use authorisation from various countries' regulatory bodies. Nonetheless, vaccines are only to prevent the disease rather than treating COVID-19. Thus, for infected patients,some of the off-label pharmacotherapies used in management of COVID-19 patients include dexamethasone, remdesivir, lopinavir-ritonavir, azithromycin, convalescent plasma, interleukin-1 inhibitors, interleukin-6 inhibitors besides life support oxygenation and ventilation if necessary.[4,5]

Traditional Chinese medicine (TCM) is included as one of the treatment options of COVID-19 guideline endorsed by the National Health Commission of the People’s Republic of China since the third version to the current eighth version.[6,7] TCM, as documented in the Chinese National Health Commission guideline, has been used in previous viral diseases including SARS and H1N1 influenza which shown beneficial therapeutics and preventive potentials.[8] Small number of COVID-19 patients have improved clinically when treated with TCM in combination with Western medicines

including the usual antiviral and supportive care.[9,10]

Under the analogue of TCM, COVID-19 belongs to the “plague” category, a febrile disease caused by “dampness pathogen” with “dampness, heat, poison, blood stasis and deficiency” as the core pathogenesis.[11] After entering the body via mouth and nose, the “evil Qi” blocks the “Qi” mechanism resulting in various symptoms commonly manifested in COVID-19 including dry cough, shortness of breath and gastrointestinal disturbances. Syndrome differentiation and treatment based on the stages are the basis in treatment of COVID-19 using TCM. TCM aims to “support the healthy, eliminate the evil and keeping the same strain,” “restricting cytokine storm and serious development of the disease,” decreasing abnormality due to hormones and drugs besides reducing mortality rate and etc.[12]

Other than being used as flavoring agent in beverages, candies, drugs, chewing gums, tobacco and toothpaste, licorice has also been used as a herbal remedy to enhance well-being and provide energy, besides treating various ailments, such as bronchitis, gastrointestinal, and upper respiratory tract infections, although its efficacy in the management of these conditions has not been adequately studied. Indeed, it has been well documented that licorice is one of frequently used medicine in normal daily TCM prescriptions.[13] Hence, it is interesting to see licorice is ranked in the top 10 herbs with highest usage frequency for all stages of COVID-19 besides being most frequently used in total.[6] Therefore, the high occurrence and frequency of GR in concoctions have kept researchers curious of its importance and roles in functionalities of health promoting effects in COVID-19 patients. Therefore, crucial and detailed information about GR will be covered by providing relevant necessary information to further its study in a more rapid manner.

Licorice

Historically, licorice has been used as sweet beverage by Egyptians and Assyrians BC. It was also introduced into the UK and turned into Pontefract cake and licorice candy. In the United States, licorice were brought by early settlers and ever since that, a variety of licorice products have been produced and imported. Twizzies, a leading licorice candy brand has recorded US$214.9 million of sales in the year 2019.[14] Aside being used as sweetener, licorice has been used in TCM and Indian Ayurvedic medicine for several thousand years in Eastern culture. Licorice is a commonly used herb in TCM however, it is usually used in combination with other herbs. According to a report from the State Council Information Office of the People’s Republic of China, the annual sales revenue of TCM is expected to be more than $434 billion by year 2020 as the use of TCM is expanding globally, currently practiced in 183 countries and regions

and growing.[15] Chemically, licorice is sourced from Glycyrrhizae Radix Et Rhizoma, Glycyrrhiza uralensis Fisch, Gycyrrhiza inflata Batalin, Glycyrrhiza glabra L., whereas the parts used as medicine are the rhizomes and dry roots of the legume or perennial herb.[1] The most active components of licorice are the flavonoids and terpenes/saponins.[3] Flavonoids consist of 1) isoflavones like formononetin and ononin, 2) flavanones like liquiritin and liquiritihenin and 3) flavones like 4',7-dihydroxy-flavone and liquiritinapioside and 4) chalcones like isoliquiritigenin and isoliquiritin.[3] Terpenes/saponins consist of tricyclic triterpenes like glycyrrhizic and glycyrrhetinic acid.[3] With that, the most reported constituents of GR are liquiritin and glycyrrhizic, which have huge roles in the activity of GR.[2,3] With reference to Table 1, GR is one of the medicines found in Qing-Fei-Pai-Du decoction, a TCM prescription recommended as COVID-19 treatment regardless of disease stage or regional status by the National Health Commission of China.[6,7]

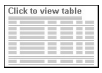

Table 1. List of Formulations Containing *Glycyrrhizae Radix Et Rhizoma* Prescribed With Its Amount According to the Classification and Symptom Differentiation in COVID-19 patients.[6,7]

Potential Mechanisms of Actions

Potential targets of COVID-19 therapies can be mainly categorized in 2 parts; 1) human innate immune system and 2) targeting the coronavirus by blocking viral RNA synthesis, viral replication, self-assembly and binding to human cell receptors. Given that research on Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) is limited and on-going, results from research on SARS-CoV-1 can act as reference due to similarity of 80% genome sequence identity between human SARS-CoV-1 and SARS-CoV-2. Virtual stimulations are alternatives to analyze and predict bioactivity of licorice. These information are summarized in Table 1 and Figure 1.

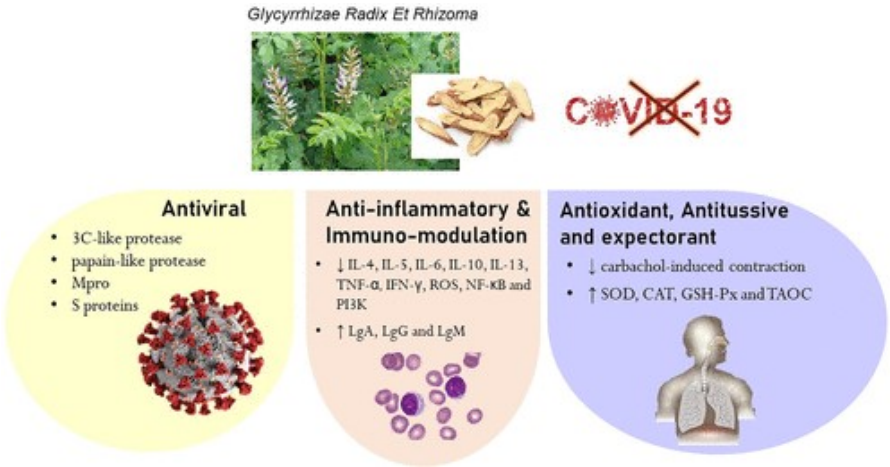

Figure 1. The summarized information of biological potentials of licorice against COVID-19.

Antiviral Activity

In order to target SARS-CoV-2, an active constituent is expected to be able to exert effect on Angiotensin-converting enzyme 2 (ACE2) probably via spike (S) proteins to prevent viral entry and/or 3C-like protease to block replication and viral assembly in host cells. A screening by Zhang and colleagues has demonstrated that licorice consists of 3 orally bioavailable, antiviral natural components against SARS-CoV-2 via inhibition of 3C-like protease, papain-like protease, Mpro and S proteins.[16,17] In context of S proteins, 3C-like protease and papain-like protease are required for host cell entry, transcription and replication of SARS-CoV-2. Network pharmacology analysis predicted one in vivo pathway related to viral infection and 6 in vivo pathways related to immune/inflammation.[17] The possible mechanism for 3C-like protease inhibition could be via targeting PIK3CG and E2F1 through PI3K-Akt signaling pathway.[16] In another in-silico approach study, derivatives of flavones and coumarin also showed strong inhibition to 3C-like protease.[18] Among the top three, rutin has been shown to bind strongly with main protease of SARS-CoV-2 via interaction with Leu141, Ser144, His163 and Asp187 amino acids residues.[19] A molecular docking has identified that kaempferol has stronger affinity with S protein of SARS-CoV-2 and ACE2 compared to a few known modern medicines in inhibiting viral infection along with the 3C-like protease inhibition.[16,20] The pathways involved in these inhibitions include JAK-STAT and PI3K-Akt signaling pathways.[16]

Licorice has been known for its viral replication inhibition for various viruses including Hepatitis B, Hepatitis C, Influenza, H1N1 and HIV as discussed by Zhong et al.[21] This information may provide hints for researchers to explore and leverage its effect further in SARS-CoV virus. Positive findings of licorice displaying antiviral activity through its glycyrrhizin compound via inhibition of replication, adsorption and penetration of the SARS-CoV virus were found.[22] A significantly potent inhibition of replication was observed; however, the exact detailed mechanism is still unclear. It is being hypothesized that glycyrrhizin was responsible for the observed effects by affecting cellular signaling pathways and increasing expression of nitrous oxide synthase.[22] A more detailed study in revealing the potential effect of small molecules on coronavirus, had showcased that glycyrrhizin derivatives exhibited activities against SARS-CoV virus at IC_{50} < 100 μM instead of previously reported as IC_{50} > 500 μM.[23] Another in-vitro study has showed that 7 glycyrrhizin derivatives blocked SARS-CoV replication at lower concentrations compared to glycyrrhizin whereas modification of the chemical structure of glycyrrhizin leads to increased anti-SARS-CoV activity from 10-times to 70-times.[24] Nonetheless, the compound baicalin was preferred than glycyrrhizin for SARS

antiviral prophylaxis or treatment as it was predicted that glycyrrhizin may not have clinically significant in vivo activities due to its low serum concentration.[25]

Anti-Inflammatory

COVID-19 patients were shown to have developed excessive inflammatory response called cytokine storm. Overactivation of immune response by high amounts of cytokines and chemokines can lead to damage in vital organs like the heart, lungs and kidneys. Thus, inhibition of inflammation-associated genes, decrease in inflammatory factors and regulation of signaling pathways and cytokines balance are paramount to prevent cytokine storm and further deterioration of COVID-19.[11]

Anti-inflammatory effects are elicited by glycyrrhizic acid via Toll-like receptor pathways by significantly decreasing IL-6 release from macrophages, thus leading to reduced cytokine storm induction.[26] Besides, glycyrrhizic acid may modify TNF and IL-17 signaling pathways and its associated pathway in overcoming COVID-19 condition.[16] Formononetin was proposed to possibly exert its anti-inflammatory action and improves immunity in COVID-19 patients via various signaling pathways; Toll-like receptor, Fc epsilon R1, ErbB, MAPK, natural killer cell mediated cytotoxicity, JAK-STAT, complement and coagulation cascades and VEGF.[3,16] Rutin has similar targeted pathways as formononetin with additional effects in targeting T cell and B cell receptor, CASP6, IL6, CCL2, IL-17, C-type leptin receptor and HIF-1 signaling pathways.[3,16] Luteolin and kaempferol played anti-inflammatory and immune-modulation effects via AKT1, RELA, STAT1, TNF, NF-Kb, VEGF, HIF-1 PTGS2, NOS2, PTGS2, MAPKs, ILs, COX-2, CASP3, EGFR, DPP4, CALM1, Toll-like receptor, JAK-STAT, T-cell and B-cell receptor and AGE-RAGE pathways.[16] β-sitosterol and licochalcone might exert effects specifically on ILs, MAPKs, CCL2, CASP3, FOS, ALB, CALM1, NOS2, PTGS2, DPP4, PTGS2.[16] Meanwhile, β-sitosterol is known to supress cytokine release, regulate immune and inflammatory responses which is deemed potential useful in overcoming the infection.[16]

In mouse macrophage RAW264.7 cells, high concentrations of licorice strongly inhibited LPS-induced nitric oxide production in concentration-dependent manner without toxicity signs.[27] Given that nitric oxide is a vital mediator in inflammation and pulmonary disease, the effect showcased in the study may imply restrictive effect specifically in halting the formation of inflammation in respiratory condition as implicated by COVID-19. Licorice's constituents, glabridin, glycyrrhizic acid and 18β-glycyrrhetinic acid had also been shown to supress inflammation via inhibition of expression and production of COX-2 genes, ILs, PGE2, TNF-α, ROS, NF-κB, PI3 K p110Ɣ and p110δ [17].

Immunomodulation

Licorice has been known to promote maturation and differentiation of lymphocytes and macrophages in order to activate the immune system. Phytohaemagglutinin-induced proliferation in human peripheral blood mononuclear cells were inhibited significantly by licorice.[27] In addition, production of TNF-α, IFN-γ and IL-10 were blocked in a concentration-dependent manner which are involved in inflammation and pathogenesis of asthma.[27] Ethanol extract of *Glycyrrhizae Radix* was shown to be able to modulate IFN-γ related autoimmune responses by decreasing number of IFN-γ T-cells, IFN-γ, IFN-γ-induced protein 10, nitric oxide production and expression of cell adhesion molecules.[28] However, another study showed an opposing effect with increased IFN-γ levels instead, in addition to inhibition of Raw and eosinophil count induced by OVA, enhancement of regulatory T-cells and reduction of IL-4, IL-5 and IL-13.[29] Isoliquiritigenin and narigenin promoted regulatory T cell induction and function both in vitro and in vivo via AKT-mTOR signaling inhibition and AhR signaling activation respectively to supress inflammation.[30] To make findings more interesting, ethanol extract of polysaccharides derived from *Glycyrrhiza glabra* were proved able to stimulate immune system via increment of serum LgA, LgG and LgM levels along with an increase in proliferation of spleen lymphocytes.[31]

Antioxidant, Antitussive and Expectorant Activities

The idea of potential roles of intervention of antioxidant activity in this disease, include assisting in reduction of positive feedback-loop in inflammation and oxidative stress processes which lead to a residing inflammation levels in patients. Traditionally, licorice has been used in bronchitis, pharyngitis, laryngitis and bronchial asthma. Meanwhile, COVID-19 patients are well known to manifest respiratory symptoms, including cough and shortness of breath. Thus, the antitussive, bronco-relaxant and expectorant activity may able to alleviate these symptoms in management of COVID-19.

Oxidative stress able to induce multiple signaling pathways, leading to an increase in inflammation. The extensive high level of inflammatory moieties may cause formation of oxidative damage in cells, leading to the development of multi-system diseases. Ethanol extract of polysaccharides derived from *Glycyrrhiza glabra* was seen to exert their antioxidant activities via increment of blood SOD, CAT, GSH-Px and TAOC activities in mice.[31] Besides, scavenging activity elicited by diphenyl picrylhydrazyl, superoxide and hydroxyl radicals were significantly found in water soluble polysaccharides isolated from *Glycyrrhiza uralensis* using DEAE-52 and Sephadex G-100 column chromatography and ethanolic extract of *G. glabra*.[32,33]

Furthermore, aqueous extract of *Radix Glycyrrhizae* showed drastic reduction of

carbachol-induced contraction in rat trachea resulting in relaxation of the bronchus possibly by blocking voltage-gated calcium ion channels.[27] Constituents of licorice such as liquiritin apioside, liquiritin and liquiritigenin showed powerful antitussive and expectorant activity.[34] At 50mg/kg, these compounds significantly reduce number of cough by 30-78%, possibly via modulation of peripheral ATP-sensitive potassium ion channel and central activation of 5-HT receptor mechanisms but not via opioid receptors.[34] On the other hand, compounds such as liquiritin apioside and liquiritin increased expectorant activities up to 2.5-folds.[34]

Safety and Adverse Effects

Licorice is categorized as moderately toxic based on its LD_{50} value and its toxicity risk is lowest when administered orally.[35] Main side effects recorded for licorice, include hypertension, fluid retention and hypokalemic-induced secondary disorders. The mineralocorticoid-like activity is due to inhibition of enzyme 11-β-HSD type 2 enzymes by active metabolites of licorice, glycyrrhizic acid glycyrrhetic acid. This lead to rise in cortisol levels and activity as conversion of cortisol to cortisone is blocked. Besides, glycyrrhetic acid also inhibits 5-β reductase activity which supresses hepatic metabolism of aldosterone Cardiomyopathy, pulmonary oedema, myoglobinuria, myopathy, cramping, seizures and rhabdomyolysis have been associated with patients following chronic, excessive licorice ingestion. Thus, it is recommended to avoid excessive intake of licorice for people aged 40 years and above, people who has history of heart disease or anyone who are more prone to cardiac arrythmias. Patients taking ACE inhibitors antihypertensive, loop diuretics or thiazides diuretics, should minimize or abstain consuming licorice due to additive potassium lowering effects from these medications and licorice, which may lead to hypokalaemia. Patients taking warfarin or digoxin should avoid licorice products completely to avoid toxicity. The use of licorice in pregnancy and neonates should be cautioned as some clinical studies showed a decrease in gestational age, preterm delivery, and changes in functions of hypothalamic–pituitary–adrenocortical axis and cognitive in delivered children when used during pregnancy.[35] Licorice also able to inhibit or induce some CYP enzymes, UDP glucuronosyltransferases, P-glycoprotein-mediated transport, 5α-reductase which may interact with other drugs when given concurrently.[35] However, when TCM consisting licorice was given to COVID-19 patients, there is no serious adverse events are being reported to date. Currently, licorice is recommended to be given as an integrative treatment with antiviral drugs in COVID-19 patients. Even though the results seem to be promising and beneficial, the reported studies only involved small number of participants and displayed a high risk of bias in term of analysis. Further clinical trials are required and ongoing to further explore the opportunities TCM and GR have

in treatment of COVID-19 [36,37]

Conclusion

Although most healthcare practitioners may feel sceptical toward TCM use, TCM should not be dismissed, especially in current context of non-existence of effective treatment for COVID-19. TCM, specifically licorice, has demonstrated potential to act as antiviral, anti-inflammatory, immunomodulation and other effects for COVID-19 patients when administered as part of concoction. Excessive use of licorice may be associated with a few known side effects like hypertension, fluid retention and hypokalaemia however, there is no serious adverse event that has been reported to date. With the background knowledge, benefits, possible mechanism of actions and safety information of licorice reviewed here, these knowledge can be further utilized as a guide in devising further studies to fully assess the effectiveness and safety of licorice in COVID-19 patients.

Authors' Note

The literature searches and data collection were performed by S.L.N. and Y.S.O. The manuscript was written by S.L.N, Y.S.O., L.C.M., H.P.G. and B.H.G. The manuscript was critically reviewed and edited by K.Y.K., N.K., V.K., S.P.T. and B.H.G. The project was conceptualized by G.B.H.

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Declaration of Conflicting Interests

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