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The potential of glycyrrhizin and licorice extract in combating COVID-19 and associated conditions

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ABSTRACT

Background: Several recent studies have stated that glycyrrhizin and licorice extract are present in most traditional Chinese medicine formulas used against SARS-CoV-2 in China. Significant data are showing that glycyrrhizin and licorice extract have multiple beneficial activities in combating most features of SARS-CoV-2.

Purpose: The aim of current review was to highlight recent progresses in research that showed the evidence of the potential use of glycyrrhizin and licorice extract against COVID-19.

Methodology: We have reviewed the information published from 1979 to October 2020. These studies demonstrated the effects , use and safety of glycyrrhizin and icorice extract against viral infections,bacterial infections, inflammatory disorders of lung (in vitro and in vivo). These studies were collated through online electronic databases research (Academic libraries as PubMed, Scopus, Web of Science and Egyptian Knowledge Bank).

Results: Pooled effect size of articles provides information about the rationale for using glycyrrhizin and licorice extract to treat COVID-19. Fifty studies demonstrate antiviral activity of glycyrrhizin and licorice extract. The most frequent mechanism of the antiviral activity is due to disrupting viral uptake into the host cells and disrupting the interaction between receptor- binding domain (RBD) of SARS-COV2 and ACE2 in recent articles. Fifty studies indicate that glycyrrhizin and licorice extract have significant antioxidant, anti-inflammatory and immunomodulatory effects. Twenty five studies provide evidence for the protective effect of glycyrrhizin and licorice extract against inflammation-induced acute lung injury and cardiovascular disorders.

Conclusion: The current study showed several evidence regarding the beneficial effects of glycyrrhizin and licorice extract in combating COVID-19. More randomized clinical trials are needed to obtain a precise conclusion.

Introduction

Coronavirus disease 2019 (COVID-19), is a kind of viral pneumonia caused by a novel coronavirus named Severe Acute Respiratory Syndrome. The pathogen that causes COVID-19 disease is a SARS-CoV2 or new coronavirus that has similar genetic structures with the other coronavirus as SARS-CoV . The SARS-CoV-2 shares 79.5% of genetic sequence and the same cell entry receptor, angiotensin-converting enzyme II (ACE2), with SARS-CoV (Zhou et al., 2020). It has an envelope spike (S) protein that is important for receptor binding and membrane fusion of coronavirus. Angiotensin-converting enzyme II (ACE2) is the cell receptor for SARS-CoV2 similar to SARS-CoV (Xu et al., 2020).

The S protein of SARS-CoV-2 has an affinity property to binds ACE2 10- to 20-fold greater than S protein of SARS-CoV. This high affinity of S protein for human ACE2 probably the reason for the rapid spread of SARS-CoV-2 (Wan et al., 2020). Hirano and Murakami (2020) documented that ACE2 as the SARS-CoV-2 receptor for cellular is critical for the virus entry. The targeting ACE2 has a promise for the prevention of SARS-CoV-2 infection during the initial phase of disease (Letko and Munster, 2020). In the later stages, a reduction of ACE2 enzyme, which

Abbreviations: : ACE2, angiotensin-converting enzyme 2; ALI, acute lung injury; ARDS, acute Respiratory Distress Syndrome; DCs, dendritic cells; COVID-19, Coronavirus disease 2019; COX-2, cyclooxygenase-2; 18β-GA, 18β-glycyrrhetinic acid; Gl, glycyrrhizin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HMGB1, high-mobility group box 1; h, hour; IL, interleukin; iNOS, inducible nitric oxide synthase; licorice extract, LE; MAPKs, mitogen-activated protein kinases; MERS, Middle East respiratory syndrome; MR, mineralocorticoid receptor; MRSA, Methicillin-resistant *Staphylococcus aureus*; NO, nitric oxide; RBD, receptor-binding domain; ROS, reactive oxygen species; S, Spike; SARS, severe acute respiratory syndrome; TCM, traditional Chinese medicine; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; TMPRSS2, type 2 transmembrane serine protease.

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leads to an increased angiotensin II concentration. This increase leads to an increased inflammatory reactions and cytokine storm as shown in COVID-19 patients. Targeting of pathways of cytokine release, especially the IL-6-STAT3 axis may be needed (Hirano and Murakami, 2020). The cytokine storm will lead to a violent attack by the body's immune system, causing Acute Respiratory Distress Syndrome(ARDS), multiple organ failure, and ultimately death in severe cases of SARS-CoV- 2 infections (Xu et al., 2020; Huang et al., 2020). SARS-CoV2 can activate the clotting chain through various mechanisms, leading to severe hypercoagulability, and ischemic changes such as ecchymosis of the fingers and toes (Li et al., 2020).

Recently, a high percentage of patients show high interest in natural medicines. This is mainly due to the general feeling that natural medicines is safer than synthetic drugs. *Glycyrrhiza glabra L.* (Fabaceae) (licorice) root is used as food and as a medicinal plant. It is native to Mediterranean areas, but it now grows in Russia, India, and China (Pastorino et al., 2018). It contains a lot of phytochemicals including more than 300 flavonoids (of them 42 chalcones) and 20 triterpenoids (Li et al., 2000). The chalcones play a crucial role in licorice's pharmacological effects (Maria Pia et al., 2019). The pharmacological values of licorice has been reported since ancient times.. The active ingredients, glycyrrhizic acid (also known as glycyrrhizin, Gl),18β-glycyrrhetinic acid(the major metaboliteof Gl), glabrin A and B, isoflavones and others have been demonstrated to have different pharmacological activities. Glycyrrhizin, an abundant bioactive component of the medicinal licorice root is rapidly metabolized by gut commensal bacteria into 18β-glycyrrhetinic acid. Licorice contains leading natural active agents, promising as a basis for developing novel antiviral agents.The most common way to extract the active ingredients of licorice root is by hot water or an ethanol / water mixture, however, other solvents are used to prepare licorice roots extracts (Tian et al., 2008). Licorice extract or its constituents suppress many RNA and DNA viruses (Fiore et al., 2008; Batiha et al., 2020). Moreover, it has been shown that a small dose of licorice extract has anti-aging activity (Reigada et al., 2020),therefore, it can eliminate the accumulation of senescent cells. Accumulation of senescent cells is the main cause of exaggeration of cytokine load or cytokine storm in elderly and obese infected by COVID-19 and an increased number of deaths. This assumption is supported by the recently published study suggesting that senotherapeutics such as azithromycin can reduce RNA virus replication in senescent cells and may have potential therapeutic activity against COVID-19 (Malavolta et al., 2020).

Traditional Chinese Medicine (TCM) has played a crucial role in treating SARS, influenza, and other acute respiratory infectious diseases (Hsu et al., 2006) . The clinical evidence has shown a good therapeutic effect for TCM in treating SARS coronaviral infections and because of the similarities in genomics, and clinical features of the COVID-19 and SARS-CoV, TCM widely used in the therapy of COVID-19. More than 85% of patients infected by SARS-CoV-2 in China have received TCM (Yang et al., 2020). Previously, treatment with TCM in SARS-CoV patients in a controlled clinical study showed a significant improvement of symptoms and shortening of the disease course (Hsu et al., 2006). The laboratory studies supported the positive clinical effect of TCM. Glycyrrhizin or licorice extract is frequently used in many preparations of TCM (Ang et al., 2020). It significantly decreased the replication of the SARS virus isolated from patients (Cinatl et al., 2003; Chen et al., 2004). However, determining its use depends on "syndrome differentiation", in which individual plans are produced for each case.

The therapeutic potential of glycyrrhizin and licorice extract for COVID-19 will be discussed in this review. This article focuses and summarizes the benefits of glycyrrhizin and licorice extract in the attenuation of COVID-19. In this review, we present preliminary data regarding the potential activity of glycyrrhizin and licorice extract against SARS-CoV-2. Potential therapeutic effects of glycyrrhizin and licorice extract and boswellia serrate gum will be evaluated in a pilot clinical study as complementary intervension for COVID-19 in Egyptian patients (ClinicalTrials.gov Identifier: NCT04487964).

Therapeutic basis of the potential use of glycyrrhizin and licorice extract against SARS-CoV-2.

Glycyrrhizin and licorice extract have been deeply and widely studied for their various activities. According to these research studies, glycyrrhizin and licorice extract have a wide range of pharmacological activities such as anti-inflammatory, antioxidative, antiviral, anticancer, antimicrobial, antidiabetic, immunomodulatory, acute lung injury prevention, cardioprotective and hepatoprotective activities (Wang et al., 2020; Editorial: Nat Plants., 2020). We will discuss and evaluate the different effects of glycyrrhizin and licorice extract that can be used to combat SARS-CoV-2 and neutralize any tissue destructive effects of the virus.

Antiviral effect of glycyrrhizin and licorice extract

Several review articles concluded that the antiviral activity of licorice extract and glycyrrhizin has been reported against various viruses including SARS-CoV and SARS-CoV2 (Wang et al., 2015a; Pastorino et al., 2018; Sun et al., 2019; Bailly and Vergoten, 2020). Licorice extract has been documented to inhibit the growth of viruses and exhibit potent inhibitory activity against virus entry. In past years, Pompei et al. (1979) published the first study demonstrating the efficacy of licorice extract against viruses. It reported that components of *Glycyrrhiza Glabra* root extract inhibit the growth and cellular diseases of many unrelated RNA viruses. Water extract from licorice shows antiviral activity against several viruses such as the human respiratory syncytial virus (HRSV) (Feng et al., 2013), and Enterovirus 71 in a human foreskin fibroblast cell line (Kuo et al., 2009). It reduced HRSV infection to a large extent by inhibiting viral attachment, uptake and stimulation of IFN secretion. However, the alkaline extract of licorice root shows higher anti-HIV activity than the aqueous extract (Ohno et al., 2014; Fukuchi et al., 2016). Also, methanol extract from licorice root was found to have more anti-hepatitis C virus activity than glycyrrhizin (Adianti et al., 2014), While ethanol extract of licorice has shown an important property to inhibit RANTES secretion by H1N1-infected A549 bronchial epithelial cells (Ko et al., 2006). Moreover, randomized controlled trials confirmed that licorice extract reduces liver cell damage in chronic hepatitis B and C (Fiore et al., 2008). Recently, it was found that licorice extract can be a strong inhibitor of the Main Protease of SARS-CoV2, but glycyrrhizin has a high binding affinity and good ADMET(Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties than other ingredients of licorice (Srivastava et al., 2020).

The active ingredients of licorice extract that have antiviral activity include certain triterpenoids, flavonoids, and oleanane-type triterpene saponins (Wei et al., 2014). Glycyrrhizin, glycyrrhetinic acid, and its derivatives are the main triterpenoid active components of licorice extract. These compounds have broad-spectrum antiviral activity against many RNA and DNA viruses such as SARS coronavirus, herpes virus, HIV, hepatitis virus, influenza viruses, cytomegaloviruses, and respiratory syncytial virus (Pu et al., 2013; Wang et al., 2015a; Pastorino et al., 2018; Batiha et al., 2020) (Tables 1 and 2). Different studies have suggested that two triterpenoids of licorice are mainly responsible for the antiviral activity reported: glycyrrhizin and 18β-glycyrrhetinic acid (Wang et al., 2015a; Pastorino et al., 2018). Glycyrrhizin suppresses many RNA and DNA viruses (Baltina et al., 2009). These compounds were found to be effectively preventing the early stage of virus infection by affecting viral attachment and penetration. Glycyrrhizin may act through affecting many cellular factors, as casein kinase II, protein kinase II and transcription factors (activating protein I and nuclear factor-kB) (Baltina et al., 2009).

Glycyrrhizin was found to be effective against viral hepatitis. It prevents the early stage of HCV- infection through affecting viral attachment and penetration. Glycyrrhizin is used clinically in the therapy of chronic viral hepatitis B in Japan and China for about 40 years (Sato et al., 1996; Sun et al., 2019). An anti-HBV mechanism of glycyrrhizin is through affecting the hepatitis B surface antigen (HBsAg). It reduced

Table 1
Antiviral activity and mechanism of action of licorice extract in articles published from 2006 to 2020.

Extract	Method of research	Major finding	Mechanism of actions	References
Licorice extract 95% ethanol extract of Glycyrrhiza 'uralensis'	H1N1infected human bronchial epithelial cells (A549).	Inhibition of influenza A virus (H1N1).	Inhibit RANTES secretion.	Ko et al., 2006.
Licorice extract	Randomized controlled trials	Reduced hepatocellular damage in chronic hepatitis B and C.	Reduced transport to the membrane.	Fiore et al., 2008.
Aqueous extract of Glycyrrhiza uralensis.	Human foreskin fibroblast cell line.	Inhibited enterovirus 71.	By preventing viral attachment and penetration.	Kuo et al., 2009.
Hot water extracts of licorice	Human Respiratory Tract Cell Lines.	Anti-Viral Activity Against Human Respiratory Syncytial Virus. Aquous ext., are highly effective against HRSV infection on airway epithelial cells.	By preventing viral attachment, internalization, and by stimulating IFN secretion.	Feng et al., 2013
Licorice extract	HCV cell culture system.	It has anti-HCV more than glycyrrhizin.	Unknown	Adianti et al., 2014
Licorice extract	Cell line	Superiority of alkaline extraction over water extraction as anti-HIV.	Unknown	Ohno et al., 2014
Licorice extract rich Oleanane-Type Triterpene Saponins	MDCK cells	Inhibit many virus.	Inhibition of neuraminidase.	Wei et al., 2014
Licorice extract rich oleanane-type triterpenoid saponins.	Cell line	In vitro anti-influenza virus activity comparable to and even higher than that of oseltamivir.	Suppression of virus release by GL treatment may be due to its inhibitory effect on PLA2G1B.	Song et al., 2014
Alkanine extract & water extract of licorice root	Cells line	Alkaline extract was highly effective against HIV and more than aquous extract. While aquous extract was more effective against HSV-infected cells.	Unknown	Fukuchi et al., 2016
Licorice extract and bioactive ingredients	Molecular Docking and ADMET Study	Inhibitor SARS-CoV2 while Gl better ADMET.	Potential to be strong inhibitors for Main protease of SARS-CoV2.	Srivastava et al., 2020

transport to the membrane and sialylation of the hepatitis B virus surface antigen (Sun et al., 2019). Glycyrrhizin has been used also, by I .V. injection to treat hepatitis C in Japan. Few adverse reactions and significant inhibition in the progression of cirrhosis and hepatocarcinoma were observed after the use of glycyrrhizin (Matsumoto et al., 2013; Pastorino et al., 2018). The mechanism of glycyrrhizin against hepatitis C virus (HCV) was through targeting the release step in which hepatitis C viral particles infect cells (Matsumoto et al., 2013).

Regarding respiratory syncytial and influenza virus, Michaelis et al. (2011) observed that glycyrrhizin induces antioxidative activity in H5N1 influenza a virus-infected cell and therefore, it inhibits virus replication. Other investigators (Wolkerstorfer et al., 2009; Baltina et al., 2015) confirmed that glycyrrhizin inhibits influenza A/H1N1 by the prevention of virus uptake into the cell. The antiviral activities of glycyrrhizin against SARS-associated coronavirus and influenza virus have also been demonstrated (Hoever et al., 2005; Baltina et al., 2015; Ang et al., 2020; Ahmad et al., 2020). The antiviral mechanisms of glycyrrhizin are through inhibiting the uptake and penetration of the virus in the early stage of the life cycle. Glycyrrhizin was highly effective when given during and after the uptake period of the virus; it exhibits the highest antiviral activity (Ang et al., 2020). Additionally, it has been shown that glycyrrhizin induced the production of a higher amount of Beclin 1 and showed an improved antiviral effect in resistance virus strain, therefore, the prophylactic activity of glycyrrhizin and licorice extract could perhaps also be extended to important human pathogenic viruses (Laconi et al., 2014).

Recently, some studies suggested that glycyrrhizin and licorice extract have the potential benefits against novel coronavirus through binding with ACE2 then inhibiting the virus absorption and penetration. Glycyrrhizin is one of the new treatments used for COVID-19 in China (Zhang and Liu, 2020). Additionally, based on the similarities between SARS-CoV with SARS-CoV-2 and the benefit of glycyrrhizin use against SARS-CoV, Many investigators suggested that glycyrrhizin has therapeutic potential against COVID-19 by binding to ACE2, and preventing the 2019-nCoV bind to ACE2 and virus absorption into the cell (Luo et al., 2020). Moreover, Murck (2020) proposed that glycyrrhizin and its metabolites have two mechanisms in combating COVID-19 through direct inhibition of expression of type 2 transmembrane serine protease (TMPRSS2), which is necessary for virus entry and activation of MR (mineralocorticoid receptor), thus reducing the expression of ACE2 protects members from being linked to COVID-19. Interestingly, It was reported that glycyrrhizic acid (glycyrrhizin) has the highest activity in disrupting the interaction between receptor- binding domain (RBD) of SARS-COV2 and ACE2, therefore, it has broad spectrum anti-coronavirus (Yu et al., 2020).

Certain derivatives of the glycyrrhizic acid (glycyrrhizin) have been shown to have a tenfold increase in the antiviral activity (Xiao et al., 2018). The anti-SARS-CoV activity of glycyrrhizic acid (glycyrrhizin) was shown to be increased up to 70-fold by conjugation of glycyrrhizin with an amide or two amino acid residues, however, the cytotoxicity also increased resulting in a decrease in the selectivity index (Hoever et al., 2005). Recently, it has been observed that glycyrrhizic acid derivatives were observed as Dengue virus inhibitors (Baltina et al., 2019). More recently, Tong et al.,(2020) observed that glycyrrhizic-Acid-Based Carbon Dots (Gly-CDs), semisynthetic derivatives of glycyrrhizic acid, possess multisite viral inhibition and unusual antiviral activity, providing

Table 2
The antiviral activity and mechanism of action of glycyrrhizin (Glycyrrhizic Acid) and its various derivatives in articles published from 1979 to 2020.

Glycyrrhizic Acid and its derivatives	Method of research	Major finding	Mechanism of actions	References
Glycyrrhizic acid	Cell culture	Inhibits growth and cytopathology of several unrelated DNA and RNA viruses, while not affecting cell activity and ability to replicate.	Unknown	Pompei et al., 1979
Glycyrrhizic acid	Cell culture		Unknown	Pompei et al., 1980
Glycyrrhizin	Cell line		Inhibit RANTES secretion.	Sato et al., 1996
Ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin	MT-4 and MOLT-4 cells	Inhibits the growth of several DNA and RNA viruses in cell cultures and inactivates Herpes simplex 1 virus irreversibly.	Unknown	Cinatl et al., 2003
Glycyrrhizic Acid Derivatives	Two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients with SARS	Suppress hepatitis B virus. glycyrrhizin administered intravenously might bind to hepatocytes at the concentration at which glycyrrhizin could modify the expression of HBV-related antigens on the hepatocyte .	The mechanism of glycyrrhizin's activity against SARS-CV may be through Glycyrrhizin affects cellular signaling pathways such as protein kinase C; casein kinase II; and transcription factors such as activator protein 1 and nuclear factor κB.	Hoever et al., 2005
Glycyrrhizin	Human Respiratory Tract Cell Lines			Wolkerstorfer et al., 2009
Glycyrrhizin				Michaelis et al., 2011
Chalcones isolated by bioassay-guided fractionation of acetone extract of Glycyrrhiza 'inflata.' .	Lung epithelial (A549) cells	Of all the compounds, glycyrrhizin was the most active in inhibiting replication of the SARS-associated virus.	The antiviral activity is mediated by an interaction with the cell membrane which most likely results in reduced endocytotic activity and hence reduced virus uptake.	Dao et al., 2011
	Porcine reproductive and respiratory syndrome virus (PRRSV).	Modified glycyrrhizin has 70-fold increased activity against SARS-CoV but also increased cytotoxicity.		Ashfaq et al., 2017
Glycyrrhizin				Hardy et al., 2012
18β-glycyrrhetinic acid (GRA) and Glycyrrhizin (GA)	HCV infected liver cells	It has antiviral effect and this inhibitory effect was abolished by treatment 1 h after virus infection.	Inhibition of H5N1-induced formation of reactive oxygen species and (in turn) reduced activation of NFκB, JNK, and p38, redox-sensitive signaling events known to be relevant for influenza A.	Matsumoto et al., 2013
	MDCK cells			Yu et al., 2014
Glycyrrhizin	A/WSN/33 (H1N1) virus using the cytopathic effect assay.	It inhibited H5N1-induced expression of the pro-inflammatory molecules CXCL10, interleukin 6, CCL2, and CCL5 and interfered with H5N1 replication.		Laconi et al., 2014
Pentacyclic triterpenes,glycyrr.				Duan et al., 2015
Licorice triterpene glycyrrhizic acid (GRA	Cell culture-produced HCV (HCVcc.	Strong inhibitory effects on influenza viral strains, H1N1, H9N2, novel H1N1 (WT), and oseltamivir-resistant novel H1N1and	Neuraminidase inhibitors	Baltina et al., 2015
Glycyrrhizin	Balb/C mice	synergistic effect with oseltamivir.	GL dose dependently inhibit the expression of HCV 3a core gene both at mRNA and protein levels.	Chen et al., 2017b
Gycyrrhizic acid derivatives	Cultured human cells		Inhibitory effects on various neuraminidases.	Si et al., 2018
Glycyrrhizic acid	MARC-145 cells infected with porcine reproductive and respiratory syndrome virus (PRRSV).	GL inhibit HCV full length and function in a dose dependent manner and had synergistic effect with interferon.	Due to its inhibitory effect on PLA2G1B(phospholipase A2 of group 1B PLA2	Liang et al., 2019
Triterpenoids		GRA, but not GA, has significant antiviral activity against rotavirus replication in vitro,	Triterpenoids bind tightly to the viral envelope hemagglutinin (HA), disrupting the interaction of HA with the sialic acid receptor and thus the attachment of viruses to host cells.	Baltina et al., 2019
Water-Soluble β-Cyclodextrin-glycyrrhetinic Acid Conjugates	Porcine kidney (PK-15) cells,	Treatment of HCV-infected Huh7 cells caused a reduction of infectious HCV production. combination treatment with GL augmented IFN-induced reduction of virus in the HCVcc system.	GRA induced a Beclin 1 production that was more than twofold higher than that produced by rapamycin, GRA is a strong inducer of the autophagy activator	Gao et al., 2020
Glycyrrhizic acid (GL) derivatives	African green monkey kidney (Vero) cells,		Beclin 1, which establishes a resistance state to HSV1 replication.	Tong et al.,(2020)
Glycyrrhizin	Sprague–Dawley	Exhibited good inhibitory activities against the influenza virus A/WSN/33 (H1N1) in MDCK cells and showed anti-HIV activities.	Gycyrrhizin mainly inhibits the penetration stage, and has little effect on the steps of adsorption or release of PRRSV in its life cycle.	Chen and Du, 2020
Glycyrrhizic-Acid Based Carbon Dots	Cell lines		With multisite inhibition mechanisms.	
Glycyrrhizin	Many celllines as Human embryonic kidney (293T cells).	GRA demonstrated a strong antiherpes simplex virus type 1, (HSV1) activity, resistance typewhereas rapamycin had no activity.	Synergistic actions were primarily due to the inhibitory effect of glycyrrhizic acid on MRP4 and BCRP, which transport Entecavir out of hepatocytes.	
	Cell lines		Triterpenoid block the entry of many viruses by capturing the HR2 domain prevalent in viral envelopes.	
	Infected DENV type 2 (DENV2) in Vero E6 cells.	Glycyrrhizin significantly reduced PRRSV proliferation and PRRSV-encoded protein expression in a dose-dependent manner.	Unknown	
	Cell line		May through interaction with DENV2 targets like NS2B-NS3 protease, NS3 helicase, and NS5 RNA-dependent RNA polymerase.	
	MOCK infected cells	GL derivatives are potent as anti-influenza A/H1N1 agents.	Glycyrrhizin inhibited PEDV infection and decreased proinflammatory cytokine secretion via the HMGB1/TLR4-mitogen-activated protein kinase (MAPK) p38 pathway.	
	Molecular docking study	Entecavir and glycyrrhizic acid combination but not Glycyrrhizin produce synergistic anti-HBV activity.	Host receptor for 2019-nCoV Angiotensinconverting enzyme 2 (ACE2), is the same as the host receptor for SARS-CoV. Gycyrrhizin.	
		Effective against Ebola, Marburg, HIV, and influenza A, triterpenoids are viral fusion inhibitors.	Unknown	
		Findings suggested that GA could be used as a lead compound for the development of potential anti-influenza virus agents.		
		GL conjugates were found as potent anti- Dengue virus.		
		Glycyrrhizin (GLY) inhibited porcine epidemic diarrhea virus (PEDV) infection,		
		Gly-CDs possess extraordinary antiviral activity, providing a promising candidate for treatment of respiratory syndrome virus infection.		
		Has potential anti-2019-nCoV and may prevent the 2019-nCoV infection.		

a promising antiviral agent for the treatment of respiratory syndrome virus infection. Also, other studies reported that glycyrrhizin could be used as a parent compound for the development of new anti-influenza virus agents (Liang et al., 2019). More recently, Ding et al. (2020) reported an interesting clinical investigation of a patient who was suffering from severe COVID-19 recovered after treatment with diammonium glycyrrhizinate (DG), a derivative of glycyrrhetinic acid. They suggested that combining DG with vitamin C might be a promising an alternative treatment for severe symptoms of COVID- 19 during quarantine.

Prevention of COVID-19-induced secondary bacterial infection by glycyrrhizin and licorice extract

Viral respiratory infections often lead to bacterial pneumonia.Therefore, antibacterial agents have become a popular treatment for COVID-19 patients in combination with antiviral agents (Hendaus et al., 2015). In uncontrolled studies that appeared to show the combination of hydroxychloroquine, azithromycin was effective in COVID 19 (Gautret et al., 2020).

Many studies observed that flavonoids/triterpenoid of licorice extract has bacteriostatic at low concentration or bactericidal at high concentration for many gram-positive and gram-negative bacteria in vitro and in vivo. It has been observed that ethanol and methanol extracts of licorice have potential antibacterial activity in vitro against many gram-positive and gram-negative bacterial strains (*Salmonella tophi, Staphylococcus aureus, Escherichia coli, Vibrio cholera, Bacillus cereus,* and *Bacillus subtilis* strains). The components detected in the ethanol and methanol extracts responsible for the antibacterial activity are flavonoid as chlorogenic acid, caffeic acid, quercitin, myricitin, kaempferol (Sedighinia et al., 2012). Licorice ethanol extract significant inhibited *Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, Klebsiella pneumonia*, and *Bacillus*. The highest inhibition zone is observed on *Streptococcus pyogenes* (Alwan et al., 2015). The aqueous extract was less effective than ethanol extract (Shirazi et al., 2007; Zhou et al., 2019). Importantly, microbial resistance to antimicrobial drugs is a matter of great clinical importance; therefore, we will evaluate the antibacterial activity of licorice extract, flavonoids and triterpenoid content against resistant microorganisms such as *Streptococcus, Staphylococcus aureus* and *Pseudomonas aeruginosa*

Streptococcus pyogenes is a common cause of upper respiratory infections. Ethanol or aqueous extracts of licorice showed marked antibacterial activities against *S.* pyogenes isolates from the throat of infected patients., however, ethanol extract was found to be two-fold more effective than aqueous extracts (Kazia et al., 2014). .Many components of licorice were tested separately against *S. pyogenes.* Licoricidin, a flavonoid constituent was found to have the highest antibacterial activity against the bacterial of the upper respiratory tract such as *Streptococcus pyogenes, Moraxella catarrhalis*, and *Haemophilus influenza*. The coumarin components such as glycycoumarin, glycerol, and glycerin exhibit moderate antibacterial activity against bacteria of the upper respiratory airway tract (Tanaka et al., 2001). Recently, Wijesundara and Rupasinghe (2019) assessed many hot aqueous infusions from different herbs (13 herbs) against *Streptococcal pharyngitis*. Aqueous infusion of licorice root showed the highest activity and the lowest minimum inhibitory concentrations. Additionally, the hot aqueous infusions of licorice showed inhibitory activity on biofilm formation resulted from *Streptococcus mutants* that cause dental caries.

The antiadherence and antimicrobial property of licorice extract on *Streptococcus mutants* in vitro was reported by many studies. Moreover, the anticarcinogenic activity of the extract of licorice has been well documented (Bhadoria et al., 2019). Alcohol licorice extract was shown to have an inhibitory effect on *Streptococcus mutants* superior to that of licorice aqueous extract or Chlorhexidine (Ajagannanavar et al., 2014). In comparison between the efficacy of licorice and propolis extract used as anticavity against *Streptococcus mutants*, licorice extract exhibited better antibacterial efficacy (Godbole et al., 2019). Licorice-containing lollipops were effective in reducing significantly salivary *S. mutants* in high caries-risk children aged 3–6 and decrease significantly the risk of dental caries in children (Chen et al., 2019). Also, in twenty patients aged between 18 and 21 years, licorice lollipop was effective in suppressing *S. mutans* and dental caries (Krishnakumar et al., 2018).

Increasing antibiotic resistance to staphylococcus aurous strains is considered the main cause of antibiotic failure. MRSA(Methicillin-resistant *Staphylococcus aureus*) has become a major source of infection in hospitals and the community. Many studies observed that licorice extract and its components have antibacterial potential against MRSA. The extract of licorice by 80% methanol exhibited potent antibacterial activity against standard *S. aureus as* well as MRSA (Lee et al., 2009). 18β-Glycyrrhetinic acid, triterpenoid of licorice, and its derivative disodium succinoyl glycyrrhetinate suppress MRSA survival and inhibit virulence gene expression but they are bactericidal at high concentrations in vitro and in vivo (Long et al., 2013; Oyama et al., 2016). Flavonoids from licorice such as glabrol, licochalcone a, licochalcone C, and licochalcone, exhibit high antibacterial activity against MRSA. Glabrol exhibited rapid bactericidal action with low levels of resistance development in vitro, so, it is a promising agent that can be used as a drug for the treatment of MRSA (Wu et al., 2019). Some studies demonstrated the effect of licorice extract or its components on the susceptibility of MRSA strains to antibiotics. Licorice flavonoids were shown to enhance the susceptibility of MRSA strains to oxacillin, a β-lactam antibiotic (Hatano et al., 2005). Screening of a 350 compound revealed that 18β-glycyrrhetinic acid (18β-GA) was the most effective component in potentiation of the antibacterial activity of certain antibiotics against *Staphylococcus aureus* and increases the bactericidal activity of tobramycin and polymyxin B against the MRSA strain (de Breij et al., 2016).

Regarding the effect of glycyrrhizin and licorice extract against *Pseudomonas aeruginosa*, the most resistant bacteria. It was documented that glycyrrhizin disturbed the permeability of bacterial membrane and efflux pump activity leading to a reduction of viability of multi-drug resistant *Pseudomonas aeruginosa*. It also reduces HMGB1 and oxidative damage. Moreover, it potentiates the effect of antibiotics like Ciprofloxacin and tobramycin against multi-drug resistant *Pseudomonas aeruginosa*. It may be used as a therapeutic for *Pseudomonas aeruginosa Keratitis* (Ekanayaka et al., 2016, 2018; Hazlett et al., 2019).

From the aforementioned studies, we suggest that the use of licorice extract or glycyrrhizin as a complementary treatment for COVID-19 can protect patients from a bacterial infection that usually occurs after a viral infection which is the main cause for severe pneumonia

Prevention of COVID-19- induced autoimmune diseases by immunomodulatory activity of glycyrrhizin and licorice extract

Licorice contains various bioactive compounds such as polysaccharides, triterpenes, and flavonoids that could enhance immunity through the activation of different targets. Early, an increase of interferon-gamma production was observed in glycyrrhizin-treated human peripheral lymphocytes in response to the surface antigen of the hepatitis B virus (Shinada et al., 1986). Also, glycyrrhizin treatment enhances the lymphocytic proliferation in response to viral infection after 4 days postinoculation (Soufy et al., 2012). Licorice extract revealed a dose-dependent cell-mediated and humeral immunomodulatory activity against mixed Eimeria infection (Hussain et al., 2017). Aqueous licorice extract increased significantly leukocyte count and phagocytic index, but the use of aqueous licorice extract with zinc displayed a more marked rise of leukocyte count and phagocytic index compared to control (Mazumder et al., 2012). 18β-glycyrrhetinic acid reduced the duration of viral antigen shedding and increases the serum antibody titers in 18β-glycyrrhetinic acid-treated animals (Hendricks et al., 2012). The mechanism of lymphoid follicles induction by 18β-glycyrrhetinic acid in the gut may through the increase of chemokine and chemokine receptor

genes expression that modulates B and T cell recruitment to lymphoid follicles (Hendricks et al., 2014). Glycyrrhizin attenuates *Salmonella enterica Serovar Typhimurium* infection in mice by promoting the release of immune factors (Xu et al., 2018a). Licorice extract, or the two components, isoliquiritigenin, and naringenin, could promote Regulatory T cells induction both in vitro and in vivo. Also, they enhanced immune suppression of Regulatory T cells. Therefore they are useful against inflammatory and autoimmune diseases (Guo et al., 2015).

Polysaccharides derived from many plants have shown to have immunostimulatory activity (Kikete et al., 2018). The polysaccharide can promote dendritic cell maturation and induce the upregulated expression of co-stimulatory molecules (Aipire et al., 2017). The low molecular weight, licorice polysaccharide displays immunomodulatory and anticancer activities. Treatment of murine bone marrow-derived dendritic cells (DCs) with licorice polysaccharide resulted in the maturation of DCs, increased the cell surface molecules expression CD80, CD86, and enhanced the expression of IL-12 p70, antitumor cytokine, by dendritic cells in a time-dependent manner (Li et al., 2012). They also increase the T lymphocytes count and thymus/spleen index. Furthermore, they decrease the pro-tumor cytokine, TNFα, and increase the levels of serum antitumor cytokines, (IL 2, IL 6, and IL 7) (Ayeka et al., 2017; Aipire et al., 2020a). Many fractions of licorice polysaccharide have been tested and only those of low molecular weight showed significant enhancement of the maturation of DCs. These fractions may be used with cancer immunotherapy to enhance the therapeutic effect (Aipire et al., 2020b). The most important action for licorice polysaccharides is the ability of the polysaccharides to enhance the anticancer cytokine IL-7, which is essential for the maturation and proliferation of immune cells and it is shown with good prognosis of cancer (Ayeka et al., 2016). Moreover, three purified licorice polysaccharides with lower molecular weight exhibited at the same concentration higher antioxidant activities (Zhang et al., 2015; Chen et al., 2017a).This antioxidant activity was highly enhanced by the selenylation modification of licorice polysaccharide (Lian et al., 2018).

Reduction of COVID-19-induced oxidative stress and inflammation by glycyrrhizin and licorice extract

A lot of studies reported that licorice extract and its constituent's triterpenes and flavonoids show evidence of anti-inflammatory activity via inhibition of TNF, MMPs, PGE2, and free radicals (Yang et al., 2017). Total flavonoids isolated from licorice and licorice extract have been observed to have anti-inflammatory effects in vitro through inhibiting iNOS, COX-2 gene, and signals of mitogen-activated protein kinases (MAPKs) (Yang et al., 2013; Vasanth et al., 2020). Total flavonoids also displayed an anti-inflammatory effect by inhibition of iNOS expression in LPS/IFN-γ stimulated RAW264.7 macrophages without cytotoxicity and regulation of ERK/NF-κB/miR-155 signaling (Jiang et al., 2018; Frattaruolo et al., 2019). The inhibitory effect of flavonoid on inflammation depends on the multi-pathway integrated mechanism. Therefore licorice flavonoid action may have high potent anti-inflammatory activity with low side effects in patients (Yu et al., 2019). Glycyrrhizin, a triterpene of licorice shows marked analgesic and anti-inflammatory effects through decreasing the expression levels of TNF-α, IL-6, iNOS, and COX-2. (Wang et al., 2015b). Due to its ability to bind the COX/mPGEs pathway for a long time, ammonium glycyrrhizinate exhibited antinociceptive and anti-inflammatory activity until 24–48 h after a single administration (Maione et al., 2019).

Flavonoids from licorice extract show marked anti-inflammatory effects in acute inflammatory models. It markedly decreased the expression of IL-1β and iNOS and reduced levels of NO and MDA at the site of inflammation (Yin et al., 2018). In the model of pancreatitis, Isoliquiritigenin suppresses oxidative stress and alleviates acute pancreatitis through modulation of the Nrf2/HO-1 pathway (Liu et al., 2018; Zhang et al., 2018a). Licorice extract and its constituents have been shown to exert therapeutic potential activity against many inflammatory diseases such as acute kidney injury. Isoliquiritigenin alleviated LPS-induced acute kidney injury by inhibition of the NF-κB pathway and TNF-alpha-induced release of HMGB (Chi et al., 2017; Tang et al., 2018). Moreover, Isoliquiritigenin ameliorates renal Inflammation and fibrosis induced by unilateral ureteral obstruction (Liao et al., 2020). It also, suppressed the Ang II-induced hypertensive renal injury via inhibiting inflammation cytokines, excessive deposition, and Nrf2 and NF-κB pathways (Xiong et al., 2018). Licorice extract suppresses inflammation that plays a crucial role in the induction of many complications to diabetes such as diabetic retina complications. Glycyrrhizin could protect the diabetic retina from vascular damage by anti-Inflammatory mechanisms through binding to an HMGB1 and inhibiting the cytokine activities (Mollica et al., 2007; Shah et al., 2018; Liu et al., 2019a, 2019b).

The antioxidant activity of glycyrrhizin/licorice extract has been documented by many investigators. Licorice extract has been used as a good source of natural antioxidants for health benefits (Velvizhiv and Annapurani, 2018). Many studies indicated that glycyrrhizin and other active components of licorice extract were found to possess excellent antioxidant activities. However, other studies found that the high content of the phenolic component in the extract of licorice is responsible for its powerful antioxidant activity (Ju et al., 1989; Visavadiya et al., 2009; Li et al., 2011; Kim et al., 2012; Zhang et al., 2019). Glycyrrhizin and licorice extract inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation that is responsible for tissue damage (Maksoud et al., 2019). The mechanism of the antiviral effect of glycyrrhizin may be through suppression of formation of reactive oxygen species induced by H5N1 and in turn, inhibits activation of p38, JNK, and NFkB in lung cells and inhibit H5N1 replication and pro-inflammatory gene expression induced by H5N1 (Michaelis et al., 2011). The correlation between doses of glycyrrhizin and licorice extract and antioxidant capacity is inconsistent. Khattab et al. (2018) suggested that the antioxidant of licorice extract at the lowest dose is more effective than the larger doses in murine model of bronchial asthma

These anti-inflammatory and antioxidant data of glycyrrhizin and licorice extract support the use of them at the early stage of infection by COVID-19 to prevent the progress of inflammation and induction of a state of hyperinflammation or cytokine storm syndrome.

The potential therapeutic effect of glycyrrhizin and licorice extract against COVID-19 induced acute lung injury(ALI)

Many active constituents of licorice root have been shown to have a therapeutic effect against acute lung injury which is the main cause of the rapid onset of acute respiratory failure (Table 3). They can be used as a novel therapeutic strategy for pulmonary inflammation (Lee et al., 2019; Shen et al., 2020). Glycyrrhizin inhibited LPS-induced ALI, the changes in lung histopathology, alveolar bleeding, and neutrophil infiltration (Ni et al., 2011). The anti-oxidative and anti-inflammatory effects of isoliquiritigenin in the lung made it able to protect the lung from injury induced by LPS. It significantly inhibited lung histopathological changes, lung inflammation, and lung injury by activating PPAR-γ and inhibiting NF-κB activation (Liu et al., 2017; Zhang et al., 2018b).

The protective effect of ethanol extract of licorice against LPS-induced acute lung injury was confirmed in mice. It reduced the level of pro-inflammatory cytokines tumor necrosis factor (TNF)-α in bronchoalveolar lavage, IL-1β, and NO in lung tissues. Furthermore, it decreased the expression of iNOS and COX-2 (Ni et al., 2011). Recent mechanism of inhibition of viral-induced inflammation and injury by licorice extract and its constituents suggested that glycyrrhetinic acid, a major bioactive hydrolysis product of glycyrrhizic acid prevents viral inflammatory injury through blocking HMGB1 cytokine activity and underlying viral-induced HMGB1-TLR4 immunological regulation axis that develops during the cytokine storm (Shi et al., 2020).

The mechanism of the protective effect of glycyrrhizin maybe also through the inactivation of the toll-like receptor (TLR) signaling pathway by suppressing TLR2 that is needed for overexpression-activated

Table 3
Protective effect of glycyrrhizin and licorice extract against acute lung injury that may occur due to COVID-19 or others in articles published from 2011 to 2020.

Active substance used	Method of research	Major finding	Mechanism of actions	References
Glycyrrhizin	Lipopolysaccharide (LPS)-induced acute lung injury (ALI) in mice.	GL potently protected against LPS-induced ALI.	The protective effects of GL may attribute partly to the suppression of COX-2 and iNOS expression.	Ni et al., 2011
Isoliquiritigenin (ISL), a flavonoid isolated from licorice.	LPS in RAW 264.7 **c**ells. & mice.	ISL significantly alleviated ALI in mice, inhibited reactive oxygen species (ROS) generation and cytotoxicity induced by t-BHP and pro-inflammatory enzymes production.	ISL activated AMPK/Nrf2/ARE signaling (survival pathway that alleviates oxidative injury) and inhibited LPS-induced NLRP3 and NF-κB activation in the lung(pro-inflammatory pathways that cause damage to cells).	Liu et al., 2017 Zhang et al., 2018a
Isoliquiritigenin ILG	Animal model of LPS-induced ALI.	ILG significantly inhibited LPS-induced lung histopathological changes. ILG inhibited the inflammatory of LPS-induced lung injury.	By activating PPAR-γ and inhibiting NF-κB activation.	Lee et al., 2019
Glycyrrhizin intraperitoneally administered	LPS-induced ALI in a mouse model.	GL can be used as a novel therapeutic strategy for pulmonary inflammation. Against ALI and acute respiratory distress syndrome (ARDS).	GL inhibited proinflammatory cytokines playing a key role in the initial phase of inflammatory response, through inhibition of the TLR-4/NF-κB signal pathway	Kong et al., 2019
Glycyrrhizin	Mice + LPS	GL reduce lipopolysaccharide-induced acute lung injury.	Glycyrrhizin inactivates toll-like receptor (TLR) signaling pathway and NF-κB pathway-related or it inhibiting TLR2 which essential for TLR activation.	Lee et al., 2019
Glycyrrhizin	LPS induce ALI in a mouse model.	Significantly alleviated lung injury in LPS-induced ALI mice.	GL inhibited proinflammatory cytokines playing a key role in the initial phase of inflammatory response, through inhibition of the TLR-4/NF-κB signal pathway	Qu et al., 2019
Glycyrrhizic acid (GA)	LPS-induced ALI in mice.	GA significantly attenuated lung injury and decreased the production of inflammatory factors TNF-α, IL-1β, and high-mobility group box 1 HMGB1.	GA inhibited the production of inflammatory factors and regulates the PI3K/AKT/mTOR pathway related autophagy.	Shen et al., 2020
Ethanolic extract of Licorice(*G. glabra*)	ALI murine models were established by intratracheal instillation of bacterial LPS.	Has protective effect on ALI in mice, inhibited pro-inflammatory mRNA expression levels, and the tissue injury.	Antiinflammatory and antioxidative stress.	Shi et al., 2020
Glycyrrhizic acid (GL), aqueous extract . Glycyrrhetinic acid (GA) is a major bioactive hydrolysis product of GL.	Murine hepatitis virus (MHV) infection model.	GA has strong hepatoprotective activity agent in hepatic infectious disease.	Not only by suppressing HMGB1 release and blocking HMGB1 cytokine activity, but also via block an underlying viral-induced HMGB1-TLR4 immunological regulation axis that occurs during the cytokine storm.	Gui et al., 2020.
Glycyrrhizin(GL)	Human alveolar epithelial cell line A549 and normal human bronchial epithelial cell line BEAS-2B	GL suppress Epithelial-mesenchymal transition (EMT) that plays an important role in fibrosis, chronic inflammation of lung.	Gl act by block Smad2/3 signaling pathway through inhibiting high-mobility group box1 (HMGB1).	Kim et al., 2020a
Glycyrrhizic acid (GA), and tilianin (TN).	Mouse model of Chronic obstructive pulmonary disease COPD.	The histolopathological lung injury was alleviated by combinational more effectively inhibited neutrophilic airway inflammation .	By regulating the expression of inflammatory cytokines and CXCL-2 by blocking the IL-17/STAT3 pathway.	Kim et al., 2020a
Approved SKBHT, berbal combination contain licorice.	Mouse model of ALI	SKBHT suppresses inflammation in the lung.	SKBHT suppressed NF-κB activity and activating Nrf2 and TNFAIP3.	

TLR signaling pathway to promote acute lung injury (Lee et al., 2019; Kong et al., 2019). Furthermore, glycyrrhizic acid can alleviate acute lung injury induced by LPS through modulating autophagy via the PI3K/AKT/mTOR pathway (Qu et al., 2019). Additionally, glycyrrhizin suppresses the epithelial-mesenchymal transition by decreasing high-mobility group box1 via the TGF-β1/Smad2/3 pathway in lung epithelial cells thereby it protects the lung from acute inflammation, fibrosis, and chronic inflammation (Gui et al., 2020).

Chinese traditional medicine as Sikyungbanha-Tang that contains many herbs in addition to licorice extract popularly is common to patients with respiratory inflammatory symptoms in China and Korea. It increases the anti-inflammatory factor through increasing the expression of genes regulated by Nrf2,therefore, it suppresses ALI in mice (Kim et al., 2020a). A herbal combinational mixture of *Glycyrrhiza glabra* and, *Agastache rugosa* extract was found to have a high inhibitory effect on neutrophilic airway inflammation by antagonizing the IL-17/STAT3 pathway. Therefore, this mixture may be used as a therapeutic agent to treat COPD(chronic obstructive pulmonary disease) (Kim et al., 2020b).

Licorice extract or its constituent popularly prescribed to patients with bronchial asthma. Glycyrrhizic acid and its dervitives were shown to have an anti-asthmatic effect in allergic asthma through the inhibition of inflammatory mediators (Fouladi et al., 2019). In a recent study randomized controlled trial, licorice extract, at a dose equivalent to 200 mg of glycyrrhizin/daily for 4 weeks, improved the pulmonary function without significant change in systolic and diastolic blood pressure or reduction in serum potassium level (Sadek et al., 2020). Licorice extract also,prevents the production of the cytokines and free radicals induced by ova albumin in a murine model of bronchial asthma (Khattab et al., 2018).

Lung injury in COVID-19 is the bad progress of the infection that leads to serious complications. Licorice in many studies was efficient to combat the developing of acute lung injury, therefore, it may be a good candidate for the prevention of acute lung injury associated with COVID-19. Moreover, it has been shown that glycyrrhizic acid and dervitives decrease mucus production by reducing MUC5AC mRNA expression in vitro and in vivo (Nishimoto et al., 2010).

The potential therapeutic effect of glycyrrhizin and licorice extract against COVID-19 induced cardiovascular disorders

Many studies demonstrated the antithrombotic effect of some ingredients of licorice extract. Isoliquiritigenin inhibits the aggregation of platelets in vitro and in vivo. The antiplatelet effect of isoliquiritigenin in vitro was similar to that of aspirin. It showed an inhibitory effect on aldose reductase in vivo with a marked inhibitory effect on platelet aggregation (Tawata et al., 1992). Glycyrrhizin was observed to have an antithrombotic effect in two models of inducing thrombosis in rats (Mendes-Silva et al., 2003). Glycyrrhizin administration preoperative could prevent venous thrombosis during the initial phase of thrombus formation by inhibition of neutrophil adhesion to venous endothelium (Nakata et al., 2008; Nakata and Kira, 2016). In a recent report, Shin and his colleagues observed that licorice root at large doses could induce intracranial hemorrhagic stroke and cerebral microbleeds due to direct inhibitors of blood coagulation factor Xa as well as of thrombin by glycyrrhizin and glycyrrhetinic acid (Shin et al., 2019).

The cardiac protective effect of licorice and its constituents were documented by several studies. Glycyrrhizic acid exhibited cardioprotective effects through the reduction of inflammation and oxidative status and modulating regulating NF-κB or Nrf2 signaling pathway (Haleagrahara et al., 2011; Xu et al., 2018b). Glycyrrhizic acid protects the myocardia from isoproterenol (ISO)-induced myocardial ischemia injury in rats through inhibition of calcium influx via L-type calcium channels (Li et al., 2019). However, Upadhyay and his colleagues suggested that the antioxidant property of licorice extract play a crucial role in the cardioprotective effect and preserving the cardiomyocytes health by licorice extract against doxorubicin-induced cardiotoxicity (Upadhyay et al., 2020). The inhibiting of oxidative stress and regulating Ca^{2+} homeostasis by L-Type Calcium Channels are responsible for the cardioprotective activity of monoammonium glycyrrhizinate injection against ISO-induced myocardial ischemia (Zhao et al., 2020).

It is clear that licorice extract and glycyrrhizin can protect COVID −19 patients from thrombus formation, microthrombus, severe hypercoagulability, and myocardial ischemia injury induced by SARS-CoV-2

Adverse reactions and contraindications of glycyrrhizin and licorice extract

Administration of high doses of licorice extract or its constituents as glycyrrhizin inhibits the 11-β-hydrogenase type II enzyme (11β-HSD2) that oxidizing cortisol to cortisone and causes pseudohyperaldosteronism. Also, Continuous inhibition of 11β-HSD2 due to excess licorice or its constituent's consumption will cause a state of hypernatremia, hypokalemia, and increased fluid volume due to water retention (Nazari et al., 2017; Deutch et al., 2019). However, The LD50 of glycyrrhizin in mice after oral administration was documented to be 14.2–18.0 g/kg (Vispute and Khopade, 2011). This figure of LD50 confirms the high safety margin of licorice. The European Union suggested a 100 mg/day as the maximum limit for consumption of glycyrrhizin (equal 60–70 g licorice) (Murphy et al., 2009). The daily doses of licorice root needed for treatment of ulcer and gastritis have been suggested to be a range between 1 and 15 g. However, higher doses for long periods may enhance the risk of hypokalemia and hypertension (Al-Snafi, 2018; Batiha et al., 2020). Moreover, Isbrucker, and Burdock (2006) proposed that the acceptable safe daily consumption of glycyrrhizin is 0.015–0.229 mg/kg body weight/day. People with kidney impairment, hypertension, and heart failure are more sensitive to the side effects of licorice and glycyrrhizin, therefore high doses and chronic use of licorice extract or glycyrrhizin are contraindicated in pregnancy, patients with hypertension, heart failure and kidney impairment, Moreover, administration of oral contraceptives, hydrocortisone, and prednisolone are contraindicated in patients used large dose of glycyrrhizin (Vispute and Khopade, 2011).

We proposed the use of a small doses of licorice extract contain 10–50 mg glycyrrhizin as a daily prophylactic dose against COVID-19. Also, a large doses of licorice extract contain 50–100 mg glycyrrhizin can be used three daily during the initial phase of disease to prevent the progress of disease and eradicate the virus. This recommendation based on FDA statement of GRAS about the safety of the chronic use of glycyrrhizin(Cosmetic Ingredient Review Expert Panel 2007). However, many investigations recommended higher doses of glycyrrhizin for inhibiting virus replication(Chen et al., 2004). In a recent report, a patient suffered from severe COVID-19 recovered after treatment with 150 mg of dimmonium glycyrrhizinate three times daily (Ding et al., 2020). Also, there are clinical trials with a dose of 300 mg orally glycyrrhizin / day, were registered on the WHO website to register clinical trials, an open-label randomized trial (ChiCTR2000029768) and a case series (ChiCTR2000030490).

Conclusions and perspectives

In the current review, we conducted a comprehensive review of recent progress in studies of the beneficial therapeutic potential, safety, and mechanism of action of glycyrrhizin and licorice extract against COVID-19. We have reviewed the information published from 1979 to October 2020. These studies demonstrated that glycyrrhizin and licorice extract has broad antiviral activity against various viruses including SARS-CoV-2 by disrupting entry of virus into host cells (ACE). Such observations have documented the efficacy of glycyrrhizin and licorice against COVID-19-induced secondary bacterial infection, autoimmune aggressive response , oxidative stress,inflammation, acute lung injury, and cardiovascular disorders. Together, this review presents important

data showing that glycyrrhizin and licorice extract have multiple beneficial activities in combating SARS-CoV-2 and most of the features of COVID-19 disease. More randomized clinical trials are needed to obtain a precise conclusion about our proposal.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Adel A. Gomaa: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Yasmin A. Abdel-Wadood:** Conceptualization, Data curation, Writing - review & editing.

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