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THERAPEUTIC PROFILE OF *Glycyrrhiza glabra*: A RAY OF HOPE IN TREATING COVID-19

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ABSTRACT

Glycyrrhiza glabra Linn (licorice) has been widely studied because of the possible ethnopharmacological benefit. It was among the essential Ayurvedic medicines studied for immunomodulatory, antiviral, antibacterial, antioxidant, hepato-protective activities. Nowadays, licorice's root parts have been evaluated to contain numerous bioactive components responsible for the treatment of respiratory tract infections and influenza-like illnesses. Most importantly, several investigations have now assessed the multiple mechanisms by which these biomolecules could attack the essential proteins and enzymes responsible for SARS-CoV-2 cellular entry and interaction. Our findings gathered that the metabolites of Glycyrrhiza glabra could interfere with COVID-19 cellular entrance and replication by blocking all five key proteins and enzymes essential for the survival and attachment of the virus. In addition to their ability to neutralise, the inflammatory cytokines storm reaction following the COVID-19 viral infection. This review was designed to digest the potential pharmacological importance of Glycyrrhiza glabra and its likeness in combating the pandemic COVID-19.

***Keywords*:** *Glycyrrhiza glabra Linn*, SARS-CoV-2, Ethnopharmacological value, COVID-19, Bioactive ingredients

INTRODUCTION

Coronavirus is a pandemic disease outbreak at the Wuhan market of China in December 2019. The pandemic COVID-19 has now infected more than 163 million people and claimed more than 3.3 million lives across 220 countries. The highest prevalence of infection was reported in the USA followed by India, Spain and Italy. At present, there is no licensed drug marketed for the treatment of SARS-CoV-2 infection (Rabaan *et al.* 2020). In the

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meantime, eight vaccines were approved for emergency use that was distributed globally for shooting amidst the pandemic. WHO reported that more than 1.5 billion vaccine doses were administered globally, in which about 369 million people were fully vaccinated (Holder 2021).

The COVID-19 vaccines are under the emergency authorisation of the FDA and the shooting is helping both asymptomatic patients and pre-infected people. However, the vaccines suffer from several limitations like lack of sufficient dose to supply the world population, therefore, only the people at the front-line risk of infection are prioritised during the vaccination initially. Although the shooting is underway with a massive record of safety, some vaccines have been reported to cause serious adverse effects and consequently, the shooting was suspended in some countries. For instance, the shooting of the AstraZeneca vaccine was suspended in some European countries (Estonia, Latvia, Lithuania and Luxembourg) over serious blood clot formation (Anon 2021a). Two severe anaphylactic reactions were reported in the UK over the use of the Pfizer vaccine (Cherry 2020). Besides, the available vaccines might be less effective against the new strength of coronavirus, as the mutation in SARS-CoV-2 spike protein (E484Q and L452R) has been reported in India (Hodgson *et al.* 2021). Moderna has announced the development of a novel form of its vaccines that can neutralise the new COVID-19 variant of South Africa (Grady, Mandavilli and Thomas 2021). The current shortage in COVID-19 vaccines supply was reported in more than 60 low-income countries amidst the pandemic. Importantly, India has reported the largest causality in the second wave of the pandemic, for being the first country to report more than 400,000 cases a day but suffered the major disruption in the vaccine supply-chain (Anon 2021b).

According to the WHO report, about three-quarters of the world populace relies solely on herbal medicines as the primary source of the remedy, because of their safety, affordability and a broad spectrum of activities (Amawi *et al.*, 2020; Rastogi, Pandey and Singh 2020). The different bioactive constituents that are traditionally known as immune-modulators and antivirals have been considered as an alternative measure of curving COVID-19 infection.

Glycyrrhiza glabra Linn (licorice) is an 'essential herbal medicinal plant' used to cure various ailments for more than 4,000 years (Dastagir and Rizvi 2016). Hippocrates had prescribed it in 400 BC for the treatment of ulcer and thirst-quenching (Lakshmi and Geetha 2011). It belongs to the family *Papilionaceae* found in abundance in tropical and subtropical regions of the world (Damle 2014). The two Greek words *Glycyrrhiza glabra,* mean sweet root. Binocularly, it was called 'licorice' in English, *Jothi-madhu* in Hindi, *Jeshthmadh* in Marathi and *Yashtimadhu* in Sanskrit (Damle 2014). Currently, more than 80% of the world population relies on traditionally based medicines (Anagha *et al.* 2014) and the number of traditional medicines users is alarmingly increasing. Consequent to the SARS-CoV-2 pandemic outbreak and the lack of allopathically approved medication or vaccine, the world relied on potential herbs known to provide potent immunomodulatory and antiviral anti-inflammatory activities (Rastogi, Pandey and Singh 2020; Amawi *et al.* 2020). Different bioactive constituents extracted from licorice were found to have shown hepato-protective, anti-inflammatory and antiviral effects, in addition to their effectiveness on the management of metabolic syndromes and oxidative stress. Hence, they have shown high tolerance and safety profile (Li, Sun and Liu 2019). The root extracts show significant potency in treating many viral infections, including SARS-CoV-2 viruses and other respiratory infectious diseases (Roshan *et al.* 2012). The exact mechanism of the antiviral activity of glycyrrhizinic acid (the main *Glycyrrhiza glabra* component) has not yet been established. Hoever *et al.* (2005) investigated the antiviral effect of glycyrrhizinic acid and found it to have doubled that

of zidovudine and twice lower than that of acyclovir. Therefore, the author's finding could be a considerable evidence of using glycyrrhizinic acid for treating COVID-19 infection.

Thus, it could be essential to benefit licorice's therapeutic variance in combating SARS-CoV-2 infections. It could be crucial to investigate the current literature on how *Glycyrrhiza glabra* could be beneficial in combating SARS-CoV-2 infections thereby exploiting the bioactive constituents responsible for the activities and the possible distinct mechanisms of action. This study focuses on finding the potential of *Glycyrrhiza glabra*, its important pharmacological activities relevant to its likeness to fight COVID-19 pandemic infection. The latest literature for the period the past 30 years to date was extracted from the official scientific database such as PubMed, Google Scholar, Research Gate and Science Direct.

Morphology of *Glycyrrhiza glabra*

Glycyrrhiza glabra is a stout herb with imparipinnate and multifoliolated leaves. Flowers are papilionaceous present in axillary spikes which are violet in colour. The reniform seeds are compressed in pods and the hardy rootstock makes numerous amounts of perennial roots. The drug (licorice) can be accumulated either in dried, peeled or unpeeled underground stems or in roots. The image of plants' leaves has been presented schematically in Figure 1.

Taxonomy of *Glycyrrhiza glabra*

Kingdome:	Plantae
Phylum:	Spermatophyte
Class:	Dicotyledonae
Domain:	Eukaryota
Family:	Fabaceae
Genus:	*Glycyrrhiza*
Species:	*Glycyrrhiza glabra*

Figure 1: Pictorial presentation of *Glycyrrhiza glabra*.

Bioactive Metabolites and Their Medicinal Importance

Licorice contains numerous bioactive metabolites that perform various pharmacological activities as depicted and compiled in Table 1. Many of the relevant metabolites are discussed in details under the applicable sub-heads.

Table 1: Licorice metabolites and their pharmacological activates

Metabolite	Compound	Formula	Pharmacological use	References
Triterpenoid saponins	Glycyrrhizin	$C_{42}H_{62}O_{16}$	Antioxidant, anticancer, sweetener, antioxidant, immunomodulatory, anti-inflammatory, hepatic- and neuro-protective and antiviral (under trial for anti-COVID-19).	(Li *et al.* 2014) (Huan *et al*. 2021).
	Glycyrrhizinic acid	$C_{42}H_{62}O_{16}$	Antiviral and anti-COVID-19 (under investigation) Immunomodulatory, anti-inflammatory, hepatic- and neuroprotective, antioxidant, anticancer, anticoagulant and antioxidant,	
	18β-glycyrrhizic acid	$C_{30}H_{46}O_4$	Anti-inflammatory and cytotoxic agent	(Ru *et al*. 2009)
	Glycyrretol	$C_{21}H_{18}O_6$	Anti-inflammatory, antidiabetic and anticancer	(Shin *et al*. 2008)
	Glabrolide	$C_{30}H_{44}O_4$	Neuroprotective, antifungal, antibacterial and antiviral	(Arif *et al.* 2020)
	Liquiritin	$C_{21}H_{22}O_9$	Antispasmodic, hepatoprotective, antioxidant, antioxidant and cardio protective	(Nakatani *et al.* 2017)
	Liquiritigenin	$C_{15}H_{12}O_4$	Post-menopausal disorder and oestrogen receptor agonist	(Arif *et al.* 2020; Matsuoka *et al*. 2019)
Flavonoids and chalcones	Isoliquiritigenin	$C_{15}H_{12}O_4$	The antagonist of NMDA receptor, GABA agonist, anti-proliferative and antioxidant	
	Licochalcone A	$C_{21}H_{22}O_4$	Pro apoptotic agent, anti-adenocarcinoma, cytochrome P450 inhibitors, antioxidant and neuroprotective	(Hatano *et al.* 1989)
	Isoliquiritin	$C_{21}H_{22}O_9$	Aldose reductase inhibitor, anti-depressant-like effect and anti-HIV	

(continued on next page)

Table 1: (*continued*)

Metabolite	Compound	Formula	Pharmacological use	References
	Glabridin	$C_{20}H_{20}O_4$	Predicted to Inhibit COVID-19 main proteases, anti-hepatocellular carcinoma, apoptosis inducer, anti-hepatitis C virus, anti-hyperlipidemia and antioxidant	(Islam *et al.* 2021; Wang *et al.* 2016)
Isoflavonoid	Prenyllico-flavone A	$C_{25}H_{26}O_4$	Anti-influenza A virus, anti-clostridium, anti-osteoporosis and sweetening agent	(Lee *et al.* 2001)
	Licoflavone A	$C_{20}H_{18}O_4$	Anti-osteoporosis and sweetening agent	(Lee *et al.* 2001)
	Licopyranocoumarin	$C_{21}H_{20}O_7$	Treatment of constipation	
Monoterpene alcohol	A-Terpineol	$C_{10}H_{18}O$	Perfumes aroma and cosmetics	(Lee *et al.* 2001)
	Licoarylcoumarin	$C_{21}H_{20}O_6$	Xanthine oxidase inhibitor and anti-HIV,	(Hatano *et al.* 1989)
Phenols	Glisoflavone	$C_{21}H_{20}O_6$	Anti-fungal and xanthine oxidase inhibitor	(Hatano *et al.* 1989)
Pyrazines	Tetramethyl pyrazine	$C_{12}H_{12}N_2O_8$	Anti-neoplastic, vasodilators, neuroprotective and anti-platelet (under trial for COVID-19 in China)	(Hao, Wu and Xu 2013; Ma *et al.* 2020)
Furan	Furfuraldehyde	$C_5H_4O_2$	Antimalarial, antidiabetic, estrogen agonist and carcinogen	(Altun and Koçer 2020)

Important Pharmacological Activities

Hepato-protective activity

Several studies have proved the hepato-protective effect of licorice. It was evident that glycyrrhizinic acid exerts hepato-protective activity by modulating the permeability of hepatocytes (Nakamura, Fujii and Ichihara 1985). Al-Jawad *et al.* (2012) evaluated the effect of aqueous root extract of licorice on acute liver injured rats by administering a daily dose of 2 gm/kg body weight orally for 1 week. The study found licorice to have shown a significant hepato-protective effect by restoring the injured rats' hepatic tissues (Rafi, Al-Jawad and Jinan 2012)). Laylani (2016) administered both aqueous and ethanolic extracts of *Glycyrrhiza glabra* at 250 mg/kg and 500 mg/kg to hepato-toxicity-induced rats. Histopathological parameters taken after 24 h injection revealed a significant reduction in liver enzymes level, thus indicating the potential hepato-protective effect of licorice (Laylani 2016). Jeong *et al.* (2002) accessed the hepato-protective activities of licorice. At the end of the study, it was found that 18ß-glycorrhizinic acid is a principally active agent behind

the therapeutic effect against licorice against liver injury, and it works by the mechanism of competitive agonism to specific glycine arginine rich (GAR) hepatic proteins.

Antioxidant activity

The flavonoids of licorice are 100 times more potent in antioxidant activities than vitamin E. It has a potential free radical cleaving effect that can be used for skin and hair protective cosmetics products (Kiso *et al.* 1984; Demizu *et al.* 1988). Numerous scientists have shown that the extract of *Glycyrrhiza glabra* has shown potential antioxidant and anti-candidate properties and thus interferes with oxidative stress induced by HIV in the HIV/AIDS treatment, it could therefore serve as a potent adjuvant agent (Aluckal *et al.* 2017). Gaitry Chopra *et al.* (2013) demonstrated the antioxidant activity of methanol extract of licorice roots at a dose of 500 µg/m, using the DPPH (1,1-diphenyl-2-picrylhydrazile) model and found that there was substantial antioxidant activity.

Anti-inflammatory

Several studies suggest that many phyto constituents of *Glycyrrhiza glabra* are potent COX-2 and phospholipase A2 inhibitors, and therefore, they might be potent anti-inflammatory agents (Pastorino *et al.* 2018; Kaur *et al.* 2010). Alcoholic extract of licorice of 200 mg/kg exerts equivalent anti-inflammatory effect to 10 mg/kg indomethacin as demonstrated on carrageenan-induced oedema rats (Gupta, Maheshwari and Khandelwal 2013). Moreover, it also illustrated an anti-inflammatory effect similar to that of hydrocortisone. Glycyrrhizinic acid is known to exhibit anti-inflammatory activity *in vivo* and work through a distinct mechanism of inhibiting pro-inflammatory cytokines (Okimasu, Moromizato and Watanabe 1983; Račková *et al.* 2007). Therefore, this could contribute to the prevention of cytokine storms caused by the SARS Cov-2 infection. An *in vivo* study performed by Matsumoto *et al.* (2013) has shown the anti-apoptotic and anti-inflammatory activity of glycyrrhizin on titanium dioxide intoxicated rats.

Respiratory diseases treatment

Glycyrrhiza glabra has shown the bronco-relaxant effect better than prednisolone and *Boswellia carterii* (Olibanum), following the trial conducted by Shi *et al.* (1998) on 54 patients, and therefore, it has been found to reduce the asthmatic attack on the tested group significantly. However, it was reported to have been a potent expectorant and demulcent agent; it stimulated tracheal mucus' secretions. The extracts and powders formulations of *Glycyrrhiza glabra* have been used in traditional settings as an antitussive and expectorant (Al-Jawad *et al.* 2012; Tsay *et al.* 2016). Azman *et al.* (2021) has proved the effectiveness of licorice in the treatment of upper respiratory tract infection, where the study indicated the 'phenyl groups' to have been a bioactive principle responsible for the antibacterial action of *Glycyrrhiza glabra*. According to the findings of a study performed by Tanaka *et al.* (2001), licorice is a potent nasal decongestant, efficacious in treating upper respiratory tract infections. Nazari, Rameshrad and Hosseinzadeh (2017) found that glycyrrhizin of 200 mg/kg enhanced the activities of respiratory tract enzymes like *superoxide dismutase, tetrahydrocannabinol* (*THC*), phenoloxidase (*PO*) and glycyrrhizin have shown to inhibit the respiratory syncytial virus (RSV) *in vitro* (Chen *et al.* 2010).

Anticoagulant

Wang *et al.* (2006) have assessed the anticoagulant activity of glycyrrhizinic acid using *in vivo* model by orally administering glycyrrhizinic acid 200 mg/kg, 300 mg/kg and 400 mg/kg, respectively to the rats 90 min before the tail cutting. The bleeding time was noted to have significantly reduced after immersing the wounded tail at physiological saline. Finally, GA was proved a competitive inhibitor of FXa (Factor Xa, enzyme belonging to the serine protease family which plays a vital role in hemostasis) in a dose-dependent manner (Wang *et al.* 2006). Jiang *et al*. (2020) virtually screened 1,571 compounds for FXa inhibitory activity, docking, pharmacophore modeling and 3D-QSAR studies performed the result obtained predicted the licorice, trifolium and olive to have been the best FXa inhibitors. Following the *in vitro* study on the different extracts of *Glycyrrhiza glabra*, the ethyl acetate extract at 3 mg/mL exhibited the highest anti-FXa activity (Jiang *et al.*, 2014; Ibrahim *et al.* 2020). Mendes-Silva *et. al.* (2003) have demonstrated the first known *in vivo* study on the antithrombotic effect of glycyrrhizin and the study result proved the compound to have possesses a promising antithrombotic impact.

Immuno stimulatory effect

Glycyrrhiza glabra extract has shown a drastic increase in the phagocytic activity of neutrophils. In contrast, the root extract was identified to elicit no immunological effect on broiler chickens (Vikhe *et al.* 2013; Moradi 2014). The mechanism of anti-inflammatory activity *Glycyrrhiza glabra* is by radical scavenging effect (Arivoli *et al.* 2012). Jassim and Naji (2003) gathered that sulfur fumigation is the ancient Chinese method of herbal drug formulation. Several investigations prove its harmful effect on the liver after long-term consumption was found to compromise the immune-modulatory effect of glycyrrhizae radix rhizome glycopeptide resistant enterococci (GRER). Furthermore, the study revealed that sulfur-fumigated-GRER caused liver damage. However, the reduction of liquiritin potency in GRER following sulfur fumigation is possibly due to the depletion of it is the immunomodulatory effect as demonstrated on cyclophosphamide immune-suppression induced mice (Jiang *et al.* 2020). The Clinical Education (2020) investigated the immunological activities of *Glycyrrhiza glabra* (Revitonil tabs) and *Echinacea purpurea* in both *in vitro* and *in vivo* models. The result obtained through *in vitro* experiments revealed that Revitonil tabs at the dose of 10 µg/mol stimulate human granulocytes 44%–53% while *Echinacea purpurea* enhanced by 15%–40% at a concentration of 100 µg/mol. Upon *in vivo* bioassay, 2.2 mg/30 mg and 1.1 mg/30mg application of Revitonil tabs and *Echinacea purpurea* was orally administered in mice, respectively. The study result indicated Revitonil tabs to be the most potent immune-modulator when compared with *Glycyrrhiza glabra* and *Echinacea purpurea* mono-extract (Clinical Education 2020).

Antiviral Activities

The extracts of *Glycyrrhiza glabra* was found to inhibit different types of viruses and the available literature indicated the two active components of *Glycyrrhiza glabra* to have been responsible for such antiviral activities, namely; 18β-glycyrrhetinic acid and glycyrrhizin acid (Yang *et al.* 2017). Omer *et al.* (2014) investigated the antiviral effect of licorice and Ribavirin against Newcastle disease, the author found that the minimal concentration of 60 mg/100 mL *Glycyrrhiza glabra* extract inhibit the viral replication processes without causing any

toxic effect. On the other hand, the concentration of 20 µg/mL of Ribavirin is the maximum safe dose for antiviral activity (Omer *et al.* 2014).

Human Immunodeficiency Virus (HIV)

Simone *et al.* (2001), prepared HIV-infected culture media of giant cells and tested the effectiveness of cochalcone A, glycocoumarin and licopyranocoumarin, the result indicated the significant inhibition of HIV growth on the giant cell. Batiha (2020), conducted an *in vitro* experiment and synthesised amides, glycopeptides and salts from derivatives of glycyrrhizin glycopeptides and biological evaluation confirmed their potency in inhibition of HIV-1 and HIV-2. Furthermore, the 'Penta-O-nicotinate' of glycyrrhizin was clinically evaluated to have anti-HIV as well as immune-modulatory activities**.** The anti-HIV activity of *Glycyrrhiza lepidota* (wild licorice) where they identified the diprenylated bibenzyl to have been the principal compound responsible for the anti-HIV activity and in contrast, glepidotin A and glepidotin B proved to be inactive against viruses (Batiha 2020).

Activity on influenza virus

Glycyrrhizinic acid and its derivatives could be a promising source of developing novel anti-influenza virus's agents. Low dose of glycyrrhizinic acid was found to promote the recovery of embrocated hen eggs infected from influenza and Newcastle disease in cell monolayer cultures. The inhibitory mechanism of glycyrrhizinic acid involves the interference with the late replication stage of the viruses rather than viral viability and virions' haemagglutination, as highlighted in Figure 3 (Ashraf *et al.* 2017; Grienke *et al.* 2014). Kim *et al.* (2011) examined the anti-H5N1 effect of injection Neo-Minophagen® approved glycyrrhizin acid derived drug. Upon evaluation, the study found that glycyrrhizin acid product inhibited influenza A virus H5N1 and its associated inflammatory induced effect without compromising natural killer (NK) cells' activities. In continuation of the earlier experiment, the author discovered the drug to inhibit inflammatory responses elicited by H5N1 influenza viruses (Kim *et al.* 2011). Therefore, glycyrrhizin acid could be a promising compound for the treatment of *H5N1* disease. Significant immune-stimulatory activity of the extract of saponin from *Glycyrrhiza glabra* L (Glabilox) demonstrated that it can serve as an adjunct for vaccination against the H7N1 influenza virus. The research compares the immune-stimulatory activity of Glabilox and Quil-A against H7N1 induced mice, and the mice were immunised subcutaneously by the formulation of both extracts. Following an animal assessment after one month of immunisation, Glabilox immunised mice showed a high level of H7N1 influenza virus-specific antibodies with no haemolytic and toxicity side-effects compared to Quil-A (Alexyuk *et al.* 2019). Moreover, Seniya (2012), virtually screened 657 phytochemical compounds from 191 antiviral plants, out of which the author identified three combinations of *Glycyrrhiza glabra* namely, licofalvone B, 2,2,4' trihydroxychalcone and davidigenin to have followed the Lipinski rule of five and excellently docked in inhibition of the active targeted site of influenza A viruses. However, the study has lacked support from animal bioassay, both *in vitro* and or *in vivo* (Oh, Barr and Hurt 2015).

Effect on human ortho-pneumovirus (HRSV)

Feng Yeh *et. al.* (2013) evaluated the anti-HRSV activity of the aqueous extract of *G. glabra*, the study result suggested that both 'Radix Glycyrrhizae' and '18β-glycyrrhetinic' increase the level of interferons and inhibit the viral cellular fusion mechanism.

Effect on hepatitis C (HCV)

According to the findings of Ashfaq *et al.* (2011), glycyrrhizin acid is very useful in targeting HCV, while showing more effectiveness in synergy with interferons.

Effect on herpes simplex virus

Ghannad *et al.* (2014) conducted an *in vivo* experiment on an animal model, and the study revealed the antiviral effectiveness of *Glycyrrhiza glabra* with specificity on 'harps simplex viral' infection through which it can be taken as a prophylactic drug. The *in vitro* study conducted by Lin (2003), revealed that 0.04 mM–0.08 mM of glycyrrhizinic acid inhibited the replication of type 4 herpes virus.

Effect on SARS-CoV-2 (COVID-19)

There are some important drug targeted sites in the SARS-CoV-2 life cycle including the cellular entry mechanism, involving angiotensin converting enzyme 2 (ACE2); transmembrane protease, serine 2 (TMPRSS2) and COVID-19 interaction. RNA transcription and replication mediated by helicase and RdRp. The means of translation and proteolytic effect of viral proteins mediate by chymotrypsin-like and papain-like proteases, in addition to virion assembling and exocytosis (Shehu *et al.* 2021). These targetable proteins are essential for curing COVID-19 with existing drugs that have therapeutic potency against these specific proteins and enzymes (Kiplin Guy *et al.* 2020).

ACE2 receptors

It has been confirmed that SARS-CoV-2 enters cells via the ACE2 receptor. This implies that the blockage or modulation of ACE2 could be a potential means to halt the cellular entry of SARS-CoV-2. The mechanism of blockage involves either inhibiting the virus ACE2-RBD interaction, directly inhibiting ACE2-receptors or using recombinant human ACE2 (rhACE2); APN01 to disrupt virus endocytosis (Heinrich, Martina and Prakash 2020).

Affecting TMPRSS2

Human TMPRSS2 more powerfully activates the COVID-19 spike protein and facilitates its flush in across the host cell membrane via ACE2 than endosomal cathepsin and other proteases enzymes. As a result, targeting TMPRSS2 may be critical for developing anti-SARS-CoV-2 molecules. Some potent TMPRSS2 inhibitors, such as camostate and bromhexine, have been shown to be repurposed against COVID-19. Stopsack K investigated the anti-TMPRSS2 activity of androgens and other corticosteroids and demonstrated their potential for repurposing in the treatment of COVID-19. Furthermore, determining the crystal structure of the TMPRSS2 protein could aid in the development of COVID-19 (Iwata-Yoshikawa *et al.* 2019).

Affecting furin

The SARS-CoV-2 S-protein possessed a furin-like cleavage site (FCS), which is responsible for the S-structural protein's form, electrostatic interaction and furin binding affinity. The study in Zhejiang province examined the effect of FCS mutation (F1-2). Hasan *et al*. (2021)

demonstrated the impact of furin-ACE2 enzyme interaction and its pathogenic role in COVID-19 infection, determining its relative proclivity to influence the structure of S-protein and the interaction between FCS and Furin.

Non-structural protein

Coronavirus possessed 16 non-structural protein (nsp) rendering varying functions, although, the specific functions elicited by nsp remain unclear. The crystal structure of nsp has been established aiding the development of novel molecules to block its action (Dong *et al.* 2020; Kandeel *et al.* 2020).

RNA-dependent RNA polymerase (RdRp)

RdRp plays a crucial role in facilitating the process of genome replication and transcription in the COVID-19 life cycle (Chan *et al.* 2020)**.** The development of the RdRp structure in complex with its cofactors (nsp7 and nsp8) is encouraging. Therefore, interfering with the function of these enzymes would help the drug design for the treatment of COVID-19 infection (McDonald 2013)**.**

The study conducted by Luo, Liu and Li (2020) concluded that at optimum dose, glycyrrhizin acid could elicit a desirable anti-COVID-19 effect and its analogs were predicted to have been more effective. Besides, the dosing of glycyrrhizin acid needs to be with caution in geriatric and in patients with heart disease (Luo Liu and Li 2020). Yonesi and Rezazadeh (2020) surveyed the available literature and confirmed the effectiveness of glycyrrhizin acid against SARS-CoV-2. However, the claim needs *in vivo* experimental support (Yonesi and Rezazadeh 2020). Chen and Du (2020) discovered glycyrrhizin acid to have worked via the inhibition of viral cellular entrance and interfere with SARS-CoV-2 receptors binding domain at minimal toxicity. The study found that molecular analogs of glycyrrhizin acid produce molecules with better antiviral potency than glycyrrhizin acid itself. However, unfortunately, found to have toxicity in the level profile (Chen and Du 2020). The molecular docking study conducted by Maurya (2020) indicated that the use of licorice may prevent SARS-CoV-2 infection by reducing the effect of cytokine storm in infected patients and boosting the body immune system. However, the findings need support of *in vitro* and *in vivo* experiments. Alternatively, *Yashtimadhu* (Telugu name of licorice) could be administered as an immunity booster as well as a prophylactic agent for mitigation and treatment of COVID-19 (Maurya 2020). Vardhan and Sahoo (2020) screened out 154 phyto-compounds from different plant sources based on a molecular docking study against five active binding sites of SARS-CoV-2. When compared with that of the FDA, the score-approved drugs, arbidol, remdesivir and hydroxychloroquine. The best 47 ligands were further screened based on drug-likeness and ADMET using *in silico* evaluation. However, the best 15 molecules were further processed to 'protein-ligand interaction' evaluations, upon which seven compounds were found to have succeeded and in overall two molecules, including glycyrrhizinic acid limuloids by having the highest binding scores of –9.9 kcal/mol and –8.2 kcal/mol, respectively. Hence, these molecules were also found to have obeyed the Lipinski rule of five; therefore, they were predicted to have higher drug-likeness properties for targeting COVID-19 (Vardhan and Sahoo 2020). Maurya (2020) evaluated the druggability of licorice's phytochemicals in terms of their binding affinities to spike protein, ACE2 enzyme, Mpro, RdRp, and furin residue of COVID-19. The docking study predicted that glycyrrhetic acid possessed the highest binding affinity to spike protein –8.3 kcal/mol, followed by shinflavanone with the binding energy of –7.8 kcal/mol and glycyrrhizin acid that has –7.2 kcal/mol, respectively. However,

the relative binding affinities of shinpterocarpin, apioside, glabridin and glycyrrhetc acid toward ACE2 enzymes are predicted to be –8.2 kcal/mol, –7.8 kcal/mol, –7.7 kcal/mol and –7.6 kcal/mol, respectively. Meanwhile, the result of binding to furin protease shows that shinpterocarpin, apioside, and glycyrrhizin acid have the highest affinity with the relative binding energies of –8.6 kcal/mol, –8.5 kcal/mol and –8.5 kcal/mol, respectively. On the other hand, glabrin B, shinflavanone and glycyrrhizic acid found to have higher binding affinities to COVID-19. Main protease (Mpro) following binding affinities; –8.9 kcal/mol, –8.4 kcal/mol and –8.2kcal/mol, respectively. Lastly, the molecular binding to 'RNA-dependent RNA polymerase' revealed that liquiritin, shinflavanone, glycyrrhizin acid and glycyrrhizic acid scored the binding affinities of –8.8 kcal/mol, –8.5 kcal/mol, –8.4 kcal/mol and –8.4 kcal/mol, respectively (Maurya 2020). Therefore, phyto-compounds of *Glycyrrhiza glabra* can target all the five active sites of SARS CoV-2, as illustrated in Figure 2.

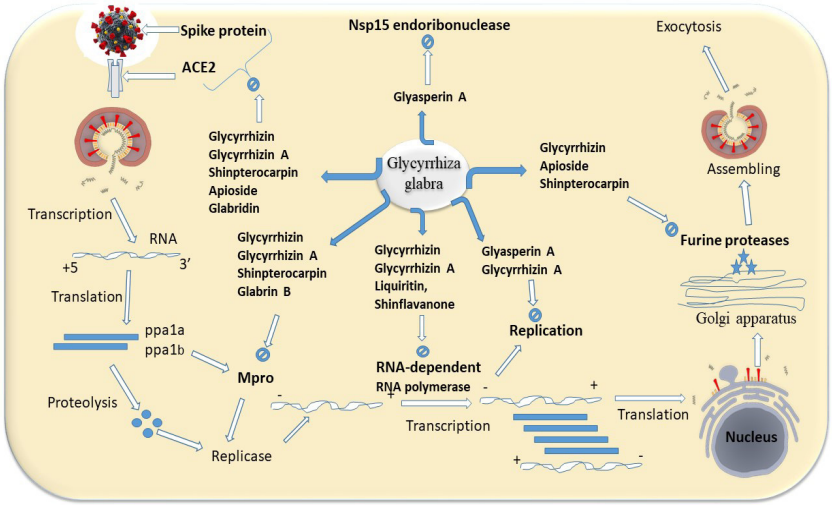

Figure 2: Different mechanism of action of *Glycyrrhiza glabra* metabolites.

Therefore, it could be a great source for the active ingredient in the drug designing of COVID-19. Sinha *et. al.* (2020) screened 20 bioactive compounds of licorice based on inhibition of COVID-19 non-structural protein (Nsp-15) and spike protein. After 'pharmaco-informatics' evaluation, glycyrrhizin acid was found to have scored the highest binding affinity to spike glycoprotein and ACE2. In contrast, glyasperin A has emerged as the molecule with the highest binding affinity to Nsp15. Thus, synergistically both these compounds can block the binding as well as the replication process of COVID-19. The author isolated numerous phyto-compounds of *Glycyrrhiza glabra* and screened them for *in silico* examination against COVID-19 inhibitory efficiency. The study was conducted by predicting the relative binding affinities of such molecules to spike glycoprotein and Nsp15 endoribonuclease of SARS-CoV-2 and comparing it with that of FDA-approved candidates Lopinavir and Ribavirin. The docking study result revealed that glyasperin A found a high affinity toward Nsp15 endoribonuclease blockage and a viral replication process. Simultaneously, glycyrrhizic acid is predicted to have a high affinity to block the COVID-19-ACE-2 receptor attachment process and thus could combat the cellular entry mechanism. However, these findings need biological validation (Sinha *et al.* 2020).

SARS-CoV-2 inhibitory mechanism of Glycyrrhiza glabra

Glycyrrhizin acid, a principal active compound of *Glycyrrhiza glabra* was reported to prevent the replication and cellular penetration of SARS-CoV-2 via indistinct mechanisms. Although, investigation shows that the nitrous oxide produced by glycyrrhizin could be responsible for inhibiting the replication of COVID-19. The pharmacological effect exerted by glycyrrhizin acid was minimal due to the rapid metabolism of the compound and this can be enhanced by the structural modification of the compound using amino acid conjugate and amides formation in the ring (Bailly and Vergoten 2020). The *in vitro* study conducted by Van de Sand *et al.* (2021) demonstrated the potential of glycyrrhizin acid to inhibit the main protease 'Mpro' (a vital enzyme responsible for SARS-CoV-2 virus replication) and halt the replication process. Glycyrrhizin acid could also prevent the cytokine storm by inhibiting the accumulation of reactive oxygen species (ROS) intracellularly. As illustrated in Figure 3, it was found to be more effective than glucocorticoids in the management of SARS-CoV infections (Van de Sand 2021). Tan *et al*. (2022) have investigated the ability of glycyrrhizin acid to bind with the ACE2 and prevent the cellular entry of SARS CoV2 clinically. The author treated the COVID-19 infected patient with diammonium glycyrrhizinate and yielded a positive prognosis (Tan *et al.* 2022).

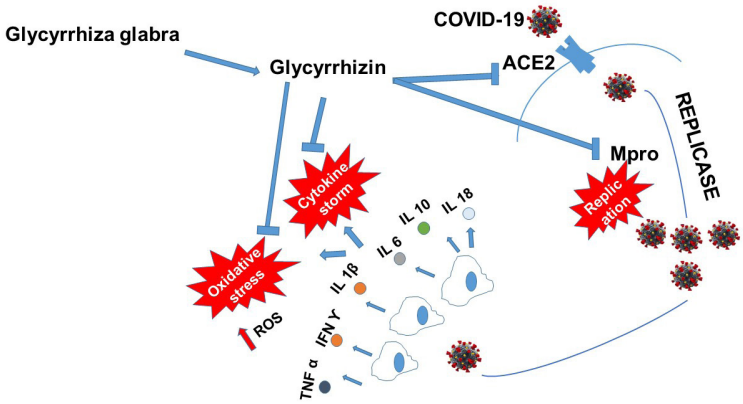

Figure 3: SARS-CoV-2 inhibitory mechanism of *Glycyrrhiza glabra*.

CONTRAINDICATIONS

Glycyrrhiza glabra has an abortifacient effect in pregnancy and thus was contraindicated in pregnancy and compromised kidney or heart, failure patients (Ramalingam *et al.* 2018). It is contraindicated to take licorice extracts along with oral contraceptives and steroids, primarily prednisolone and hydrocortisone (Batiha *et al.* 2020). Daily administration of more than 15 g may lead to a surge in blood pressure, mineralocorticoid and hyperkalemia (Kaur *et al.* 2010; Nahidi *et al.* 2012). To date, there is no clinically established dosage limit of different Glycyrrhiza constituents, efficiently alleviating the inherently associated side effects. Therefore, advanced research need to prove the optimal safety dose of licorice for other medical conditions and patient categories.

CONCLUSION

From the surveyed literature, we concluded that *Glycyrrhiza glabra* is a rich source of numerous bioactive compounds that elicit different pharmacological activities against the treatment of infections and metabolic disorders. Interestingly, it has been exploited as potent antivirals, impotently, influenza, HIV and SARS-CoV-2 related viruses, some *in silico* and few *in vivo* studies have predicted the licorice metabolites to have promising potential in targeting all the five key proteins and enzymes responsible for COVID-19 cellular entrance and replication as evident from Figure 2, even though research lacked *in vivo* support and validation. Besides, the body immune system response to COVID-19 infection in immune-compromised people results in intensive inflammatory reactions, which caused 'cytokines storm' the mechanism to lead to multi-organ damages and subsequent death. *Glycyrrhiza glabra* has the potentiality to inhibit these mechanisms because of its inherent immune-modulatory, antioxidant, anti-inflammatory, anticoagulant and other desirable therapeutic benefits. Therefore, there is a ray of hope for licorice to provide effective medications for COVID-19 infection.

Future Perspectives

The research on licorice and its bioactive constituents should be conducted extensively on animal models, both, *in vivo* and *in vitro*. Meanwhile, the clinical and pharmacokinetic validation of such ligands will pave the way for inventing novel drugs effective against COVID-19.

REFERENCES

ALEXYUK, P. G., BOGOYAVLENSKIY, A. P., ALEXYUK, M. S., TURMAGAMBETOVA, A. S., ZAITSEVA, I. A., OMIRTAEVA, E. S. *et al*. (2019) Adjuvant activity of multimolecular complexes based on *Glycyrrhiza glabra* saponins, lipids, and influenza virus glycoproteins, *Archives of Virology*, 164(7): 1793–1803. https://doi.org/10.1007/s00705-019-04273-2

AL-JAWAD, F., AL-RAZZUQI, R., HASHIM, H. & AL-BAYATI, N. (2012) *Glycyrrhiza glabra* versus *Boswellia carterii* in chronic bronchial asthma: A comparative study of efficacy, *Indian Journal of Allergy*, *Asthma and Immunology*, 26(1): 6–8. https://doi.org/10.4103/0972-6691.104437

ALTUN, Ö. & KOÇER, M.Ö. (2020) Pt (II) complex of Schiff base derived from L-phenylalanine and furfuraldehyde in the presence of 8-hydroxyquinoline: Structural analysis, composition of complex and biological activity, *Comptes Rendus Chimie*, 23(2): 127–142. https://doi.org/10.5802/crchim.9

ALUCKAL, E., ISMAIL, A., PAULOSE, A., LAKSHMANAN, S., BALAKRISHNAN, M. S., MATHEW, B. *et al*. (2017) Assessment of total antioxidant capacity and antimicrobial activity of *Glycyrrhiza glabra* in saliva of HIV-infected patients, *Journal of Pharmacy and Bioallied Sciences*, 9(Suppl 1): S237–S240. https://doi.org/10.4103/jpbs.JPBS_141_17

AMAWI, H., ABU DEIAB, G. I., ALJABALI, A. A., DUA, K. & TAMBUWALA, M. M. (2020) COVID-19 pandemic: An overview of epidemiology, pathogenesis, diagnostics and potential vaccines and therapeutics, *Therapeutic Delivery*, 11(4): 245–268. https://doi.org/10.4155/tde-2020-0035

ANAGHA, K., MANASI, D., PRIYA, L. & MEERA, M. (2014) Antimicrobial activity of Yashtimadhu (*Glycyrrhiza glabra L.*): A review, *International Journal of Current Microbiology and Applied Sciences*, 3(1): 329–336.

ANON (2021a) COVID-19: Several European countries suspend AstraZeneca vaccinations over blood clot fears [Online]. https://www.france24.com/en/europe/20210311-covid-19-denmark-pauses-use-of-astrazeneca-vaccine-over-blood-clot-fears [21 May 2021].

ANON (2021b) India coronavirus: Over-18s vaccination drive hit by shortages, *BBC News*. https://www.bbc.com/news/world-asia-india-56345591 [21 May 2021].

ARIF, N., SUBHANI, A., HUSSAIN, W. & RASOOL, N. (2020) *In silico* inhibition of BACE-1 by selective phytochemicals as novel potential inhibitors: Molecular docking and DFT studies, *Current Drug Discovery Technologies*, 17(3): 397–411. https://doi.org/10.2174/1570163816666190214161825

ARIVOLI, S., RAVINDRAN, K. J., RAVEEN, R. & TENNYSON, S. (2012) Larvicidal activity of botanicals against the filarial vector *Culex quinquefasciatus* Say (Diptera: Culicidae), *International Journal of Research in Zoology*, 2(1): 13–17.

ASHFAQ, U. A., MASOUD, M. S., NAWAZ, Z. & RIAZUDDIN, S. (2011) Glycyrrhizin as antiviral agent against Hepatitis C Virus, *Journal of Translational Medicine*, 9(1): 112. https://doi.org/10.1186/1479-5876-9-112

ASHRAF, A., ASHRAF, M. M., RAFIQE, A., ASLAM, B., GALANI, S., ZAFAR, S. *et al.* (2017) *In vivo* antiviral potential of *Glycyrrhiza glabra* extract against Newcastle disease virus, *Pakistan Journal of Pharmaceutical Sciences*, 30(2): 567–572.

AZMAN, S., SEKAR, M., BONAM, S. R., GAN, S. H., WAHIDIN, S., LUM, P. T. *et al.* (2021) Traditional medicinal plants conferring protection against ovalbumin-induced asthma in experimental animals: A review, *Journal of Asthma and Allergy*, 14(1): 641–662. https://doi.org/10.2147/JAA.S296391

BAILLY, C. & VERGOTEN, G. (2020) Glycyrrhizin: An alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome, *Pharmacology and Therapeutics*, 214(1): 107618. https://doi.org/10.1016/j.pharmthera.2020.107618

BATIHA, G. E. S., BESHBISHY, A. M., EL-MLEEH, A., ABDEL-DAIM, M. M. & DEVKOTA, H. P. (2020) Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of *Glycyrrhiza glabra* L. (Fabaceae), *Biomolecules*, 10(3): 1–19. https://doi.org/10.3390/biom10030352

CHAN, J. F., KOK, K. H., ZHU, Z., CHU, H., TO, K. K., YUAN, S. *et al.* (2020) Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan, *Emerging Microbes and Infections*, 9(1): 221–236. https://doi.org/10.1080/22221751.2020.1719902

CHEN, H. & DU, Q. (2020) Potential natural compounds for preventing SARS-CoV-2 (2019-nCoV) infection. Preprints. https://doi.org/10.20944/preprints202001.0358.v3

CHEN, X., MAI, K., ZHANG, W., WANG, X., AI, Q., XU, W. *et al*. (2010) Effects of dietary Glycyrrhizin on growth and nonspecific immunity of white shrimp, *Litopenaeus vannamei*, *Journal of the World Aquaculture Society*, 41: 665–674. https://doi.org/10.1111/j.1749-7345.2010.00409.x

CHERRY, D. S. (2020) Limitations on the COVID-19 vaccine for infection vs. disease/ herd immunity [Online]. https://www.axiomllc.com/blog/limitations-on-the-covid-19-vaccine/ [Accessed: 21 May 2021].

CLINICAL EDUCATION (2020) The role of liquorice extract in reducing the risk of COVID-19 infection. https://www.clinicaleducation.org/news/the-role-of-liquorice-extract-in-reducing-the-risk-of-covid-19-infection/ [21 May 2021].

DAMLE, M. (2014) *Glycyrrhiza glabra* (Liquorice): A potent medicinal herb, *International Journal of Herbal Medicine*, 2(2): 132–136.

DASTAGIR, G. & RIZVI, M. A. (2016) Review—*Glycyrrhiza glabra* L. (Liquorice), *Pakistan Journal of Pharmaceutical Sciences*, 29(5): 1727–1733.

DEMIZU, S., KAJIYAMA, K., TAKAHASHI, K., HIRAGA, Y., YAMAMOTO, S., TAMURA, Y. *et al*. (1988) Antioxidant and antimicrobial constituents of licorice: Isolation and structure elucidation of a new benzofuran derivative, *Chemical and Pharmaceutical Bulletin (Tokyo)*, 36(9): 3474–3479. https://doi.org/10.1248/cpb.36.3474

DONG, S., SUN, J., MAO, Z., WANG, L., LU, Y. L. & LI, J. (2020) A guideline for homology modeling of the proteins from newly discovered betacoronavirus, 2019 novel coronavirus (2019-nCoV), *Journal of Medical Virology*, 92(9): 1542–1548. https://doi.org/10.1002/ jmv.25768

FENG, Y. C., WANG, K. C., CHIANG, L. C., SHIEH, D. E., YEN, M. H. & SAN, C. J. (2013) Water extract of licorice had anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines, *Journal of Ethnopharmacol*, 148(2): 466–473. https://doi.org/10.1016/j.jep.2013.04.040

GAITRY CHOPRA, P. K. P., SARAF, B. D., INAM, F. & DEO, S. S. (2013) Antimicrobial and antioxidant activities of methanol extract roots of *Glycyrrhiza glabra* and HPLC analysis, *International Journal of Pharmacy and Pharmaceutical Sciences*, 5(2): 157–160.

GHANNAD, M. S., MOHAMMADI, A., SAFIALLAHY, S., FARADMAL, J., AZIZI, M. & AHMADVAND, Z. (2014) The effect of aqueous extract of *Glycyrrhiza glabra* on herpes simplex virus 1, *Jundishapur Journal of Microbiology*, 7(7): e11616. https://doi.org/10.5812%2Fjjm.11616

GRADY, D., MANDAVILLI, A. & THOMAS, K. (2021) As virus grows stealthier, vaccine makers reconsider battle plans, *The New York Times*. https://www.nytimes.com/2021/01/25/health/coronavirus-moderna-vaccine-variant.html [21 May 2021].

GRIENKE, U., BRAUN, H., SEIDEL, N., KIRCHMAIR, J., RICHTER, M., KRUMBHOLZ, A. *et al*. (2014) Computer-guided approach to access the anti-influenza activity of licorice constituents, *Journal of Natural Products*, 77(3): 563–570. https://doi.org/10.1021/np400817j

GUPTA, A., MAHESHWARI, D. K. & KHANDELWAL, G. (2013) Antibacterial activity of *Glycyrrhiza glabra* roots against certain gram-positive and gram-negative bacterial strains. Journal of Applied and Natural Science, 5(2): 459–464. https://doi.org/10.31018/jans.v5i2.354

HAO, F., WU, Q. & XU, Y. (2013) Precursor supply strategy for tetramethylpyrazine production by *Bacillus subtilis* on solid-state fermentation of wheat bran, *Applied Biochemistry and Biotechnology*, 169(4): 1346–1352. https://doi.org/10.1007/s12010-012-0083-0

HASAN, A., PARAY, B. A., HUSSAIN, A., QADIR, F. A., ATTAR, F., AZIZ, F. M., *et al.* (2021) A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin, *Journal of Biomolecular Structure and Dynamics*, 39(8): 3025–3033. https://doi.org/10.1080/07391102.2020.1754293

HATANO, T., YASUHARA, T., FUKUDA, T., NORO, T. & OKUDA, T. (1989) Phenolic constituents of licorice. II. Structures of licopyranocoumarin, licoarylcoumarin and glisoflavone, and inhibitory effects of licorice phenolics on xanthine oxidase, *Chemical & Pharmaceutical Bulletin*, 37(11): 3005–3009. https://doi.org/10.1248/cpb.37.3005

HEINRICH, M. A., MARTINA, B. & PRAKASH, J. (2020) Nanomedicine strategies to target coronavirus, *Nano Today*, 35(1): 100961. https://doi.org/10.1016/j.nantod.2020.100961

HODGSON, S. H., MANSATTA, K., MALLETT, G., HARRIS, V., EMARY, K. R. & POLLARD, A. J. (2021) What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2, *The Lancet Infectious Diseases*, 21(2): e26–e35. https://doi.org/10.1016/S1473-3099(20)30773-8

HOEVER, G., BALTINA, L., MICHAELIS, M., KONDRATENKO, R., BALTINA, L., TOLSTIKOV, G. A. *et al*. (2005) Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus, *Journal of Medicinal Chemistry*, 48(4): 1256–1259. https://doi.org/10.1021/jm0493008

HOLDER, J. (2021) Tracking coronavirus vaccinations around the world. *The New York Times*. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html [21 May 2021].

HUAN, C., XU, Y., ZHANG, W., GUO, T., PAN, H. & GAO, S. (2021) Research progress on the antiviral activity of glycyrrhizin and its derivatives in liquorice, *Frontiers in Pharmacology*, 12(1): 1706. https://doi.org/10.3389/fphar.2021.680674

IBRAHIM, R. S., MAHROUS, R. S., FATHY, H. M., OMAR, A. A. & ABU EL-KHAIR, R. M. (2020) Anticoagulant activity screening of an in-house database of natural compounds for discovering novel selective factor Xa inhibitors; A combined *in silico* and *in vitro* approach, *Medicinal Chemistry Research*, 29(1): 707–726. https://doi.org/10.1007/s00044-020-02516-5

ISLAM, R., PARVES, M. R., PAUL, A. S., UDDIN, N., RAHMAN, M. S., MAMUN, A. A. *et al*. (2021) A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2, *Journal of Biomolecular Structure and Dynamics*, 39(9): 3213–3224. https://doi.org/10.1080/07391102.2020.1761883

IWATA-YOSHIKAWA, N., OKAMURA, T., SHIMIZU, Y., HASEGAWA, H., TAKEDA, M. & NAGATA, N. (2019) TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection, *Journal of Virology*, 93(6): e01815–e01818. https://doi.org/10.1128/JVI.01815-18

JASSIM, S. A. & NAJI, M. A. (2003) Novel antiviral agents: A medicinal plant perspective, *Journal of Applied Microbiology*, 95(3): 412–427. https://doi.org/10.1046/j.1365-2672.2003.02026.x

JEONG, H. G., YOU, H. J., PARK, S. J., MOON, A. R., CHUNG, Y. C., KANG, S. K. *et al*. (2002) Hepatoprotective effects of 18beta-glycyrrhetinic acid on carbon tetrachloride-induced liver injury: inhibition of cytochrome P450 2E1 expression, *Pharmacological Research*, 46(3): 221–227. https://doi.org/10.1016/S1043-6618(02)00121-4

JIANG, J., XIAO, S., YAN, S., XIAO, J. & XU, X. (2020) *Glycyrrhizae radix* et rhizoma processed by sulfur fumigation damaged the chemical profile accompanied by immunosuppression and liver injury, *BioMed Research International*, 2020(1): 5439853. https://doi.org/10.1155/2020/5439853

JIANG, L., WANG, Q., SHEN, S., XIAO, T. & LI, Y. (2014) Discovery of glycyrrhetinic acid as an orally active, direct inhibitor of blood coagulation Factor Xa, *Thrombosis Research*, 133(3): 501–506. https://doi.org/10.1016/j.thromres.2013.12.025

KANDEEL, M., IBRAHIM, A., FAYEZ, M. & AL-NAZAWI, M. (2020) From SARS and MERS CoVs to SARS-CoV-2: Moving toward more biased codon usage in viral structural and nonstructural genes, *Journal of Medical Virology*, 92(6): 660–666. https://doi.org/10.1002/jmv.25754

KAUR, P., KAUR, S., KUMAR, S. & SINGH, P. (2010) *Glycyrrhiza glabra* L. medicinal plants as potential source of COX-2 inhibitors, *American Journal of Biomedical Sciences*, 2(2): 108–120. https://doi.org/10.5099/aj100200108

KIM, S. W., LIM, C. M., LEE, H. K. & LEE, J. K. (2011) The use of stronger neo-minophagen C, a glycyrrhizin-containing preparation, in robust neuroprotection in the postischemic brain, *Anatomy and Cell Biology*, 44(4): 304–313. https://doi.org/10.5115/acb.2011.44.4.304

KIPLIN GUY, R., DIPAOLA, R. S., ROMANELLI, F. & DUTCH, R. E. (2020) Rapid repurposing of drugs for COVID-19, *Science*, 368(6493): 829–830. https://doi.org/10.1126/science.abb9332

KISO, Y., TOHKIN, M., HIKINO, H., HATTORI, M., SAKAMOTO, T. & NAMBA, T. (1984) Mechanism of antihepatotoxic activity of glycyrrhizin I: Effect on free radical generation and lipid peroxidation, *Planta Medica*, 50(4): 298–302. https://doi.org/10.1055/s-2007-969714

LAKSHMI, T. & GEETHA, R. V. (2011) *Glycyrrhiza glabra* linn commonly known as licorice: A therapeutic review, *International Journal of Pharmacy and Pharmaceutical Sciences*, 3(4): 20–25.

LAYLANI, L. A.-A.-S. S. (2016) Hepatoprotective effect of *Glycyrrhiza glabra L.* extracts against carbon tetrachloride-induced acute liver damage in rats, *International Journal of Veterinary Science, Medicine & Research*, 1(1): 1–8.

LEE, S. E., KIM, J. G., LEE, J. G., LEE, J. S., IM, M. J., JEONG *et al.* (2001) The first total syntheses of prenyllicoflavone A and licoflavone S and biological evaluation as inhibitors of bone resorption pits formation, *Bulletin of the Korean Chemical Society*, 22(1): 1295–1296.

LI, J. Y., CAO, H. Y., LIU, P., CHENG, G. H. & SUN, M. Y. (2014) Glycyrrhizic acid in the treatment of liver diseases: Literature review, *BioMed Research International*, 2020(2014): 872139. https://doi.org/10.1155/2014/872139

LI, X., SUN, R. & LIU, R. (2019) Natural products in licorice for the therapy of liver diseases: Progress and future opportunities, *Pharmacological Research*, 144(1): 210–226. https://doi.org/10.1016/j.phrs.2019.04.025

LIN, J. C. (2003) Mechanism of action of glycyrrhizic acid in inhibition of Epstein-Barr virus replication *in vitro*, *Antiviral Research*, 59(1): 41–47. https://doi.org/10.1016/S0166-3542(03)00030-5

LUO, P., LIU, D. & LI, J. (2020) Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19, *International Journal of Antimicrobial Agents*, 55(6): 105995. https://doi.org/10.1016/j.ijantimicag.2020.105995

MA, J., HUO, X. Q., CHEN, X., ZHU, W. X., YAO, M. C., QIAO, Y. J. *et al.* (2020) Study on screening potential traditional Chinese medicines against 2019-nCoV based on Mpro and PLP, *China Journal of Chinese Materia Medica*, 45(6): 1219–1224.

MATSUMOTO, Y., MATSUURA, T., AOYAGI, H., MATSUDA, M., HMWE, S. S., DATE, T. *et al.* (2013) Antiviral activity of glycyrrhizin against hepatitis C virus *in vitro. PLoS ONE*, 8(7): e68992. https://doi.org/10.1371/journal.pone.0068992

MATSUOKA, S., NAKAMURA, K., OHMORI, K. & SUZUKI, K. (2019) General synthetic approach to rotenoids via stereospecific, group-selective 1,2-rearrangement and dual S_NAr cyclizations of aryl fluorides, *Synthesis (Germany)*, 51(5): 1139–1156. https://doi.org/10.1055/s-0037-1611654

MAURYA, D. K. (2020) Evaluation of Yashtimadhu (*Glycyrrhiza glabra*) active phytochemicals against novel coronavirus (SARS-CoV-2), *Research Square*, 1(1): 1–22. https://doi.org/10.21203/rs.3.rs-26480/v1

MCDONALD, S. M. (2013) RNA synthetic mechanisms employed by diverse families of RNA viruses, *Wiley Interdisciplinary Reviews: RNA*, 4(4): 351–367. https://doi.org/10.1002/wrna.1164

MENDES-SILVA, W., ASSAFIM, M., RUTA, B., MONTEIRO, R. Q., GUIMARÃES, J. A. & ZINGALI, R. B. (2003) Antithrombotic effect of glycyrrhizin, a plant-derived thrombin inhibitor, *Thrombosis Research*, 112(1–2): 93–98. https://doi.org/10.1016/j.thromres.2003.10.014

MORADI, N. (2014) Performance and some immunological parameter responses of broiler chickens to licorice (*Glycyrrhiza glabra*) extract administration in the drinking water, *Annual Research & Review in Biology*, 4(4): 675–683. https://doi.org/10.9734/ARRB/2014/5277

NAHIDI, F., ZARE, E., MOJAB, F. & ALAVI-MAJD, H. (2012) Effects of licorice on relief and recurrence of menopausal hot flashes, *Iranian Journal of Pharmaceutical Research*, 11(2): 541–548.

NAKAMURA, T., FUJII, T. & ICHIHARA, A. (1985) Enzyme leakage due to change of membrane permeability of primary cultured rat hepatocytes treated with various hepatotoxins and its prevention by glycyrrhizin, *Cell Biology and Toxicology*, 1(1): 285–295. https://doi.org/10.1007/BF00118193

NAKATANI, Y., KOBE, A., KURIYA, M., HIROKI, Y., YAHAGI, T., SAKAKIBARA, I. *et al*. (2017) Neuroprotective effect of liquiritin as an antioxidant via an increase in glucose-6-phosphate dehydrogenase expression on B65 neuroblastoma cells, *European Journal of Pharmacology*, 815(1): 381–390. https://doi.org/10.1016/j.ejphar.2017.09.040

NAZARI, S., RAMESHRAD, M. & HOSSEINZADEH, H. (2017) Toxicological effects of *Glycyrrhiza glabra* (licorice): A review, *Phytotherapy Research*, 31(11): 1635–1650. https://doi.org/10.1002/ptr.5893

OH, D. Y., BARR, I. G. & HURT, A. C. (2015) A novel video tracking method to evaluate the effect of influenza infection and antiviral treatment on ferret activity, *PLoS ONE,* 10(3): e0118780.

OKIMASU, E., MOROMIZATO Y. & WATANABE, S. (1983) Inhibition of phospholipase A2 and platelet aggregation by glycyrrhizin, an antiinflammation drug, *Acta Medica Okayama*, 37(5): 385–391.

OMER, M. O., ALMALKI, W. H., SHAHID, I., KHURAM, S., ALTAF, I. & IMRAN, S. (2014) Comparative study to evaluate the anti-viral efficacy of *Glycyrrhiza glabra* extract and ribavirin against the Newcastle disease virus, *Pharmacognosy Research*, 6(1): 6–11. https://doi.org/10.4103/0974-8490.122911

PASTORINO, G., CORNARA, L., SOARES, S., RODRIGUES, F. & OLIVEIRA, M. (2018) Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review, *Phytotherapy Research*, 32(12): 2323–2339. https://doi.org/10.1002/ptr.6178

RABAAN, A. A., AL-AHMED, S. H., SAH, R., TIWARI, R., YATOO, M., PATEL, S. K., *et al.* (2020) SARS-CoV-2/COVID-19 and advances in developing potential therapeutics and vaccines to counter this emerging pandemic, *Annals of Clinical Microbiology and Antimicrobials*, 19(1): 1–37. https://doi.org/10.1186/s12941-020-00384-w

RAČKOVÁ, L., JANCINOVÁ, V., PETRÍKOVÁ, M., DRÁBIKOVÁ, K., NOSÁL, R., STEFEK, M., *et al.* (2007) Mechanism of anti-inflammatory action of liquorice extract and glycyrrhizin, *Natural Product Research*, 21(14): 1234–1241. https://doi.org/10.1080/14786410701371280

RAFI, A. R., AL-JAWAD, H. & JINAN, A. H. (2012) Hepatoprotective effect of Glycyrrhiza glabra in carbon tetrachloride-induced model of acute liver injury, *Journal of Physiology and Pharmacology Advances*, 2(7): 259–263.

RAMALINGAM, M., KIM, H., LEE, Y. & LEE, Y. I. (2018) Phytochemical and pharmacological role of liquiritigenin and isoliquiritigenin from Radix Glycyrrhizae in human health and disease models, *Frontiers in Aging Neuroscience*, 10(1): 1663–4365. https://doi.org/10.3389/fnagi.2018.00348

RASTOGI, S., PANDEY, D. N. & SINGH, R. H. (2020) COVID-19 pandemic: A pragmatic plan for ayurveda intervention, *Journal of Ayurveda and Integrative Medicine*, 13(1): 100312. https://doi.org/10.1016/j.jaim.2020.04.002

ROSHAN, A., VERMA, N. K., KUMAR, C. S., CHANDRA, V., SINGH, D. P. & PANDAY, M. K. (2012) Phytochemical constituent, pharmacological activities and medicinal uses through the millenia of *Glycyrrhiza glabra* Linn: A review, *International Research Journal of Pharmacy*, 3(8): 45–55.

RU, R. P., ZHAO, H., CHEN, X. J. & TANG, H. Y. (2009) Investigation of anti-inflammatory effect among 18α-, 18β-glycyrrhizic acids and their different proportions in rats and mice, *Chinese Journal of Hospital Pharmacy*, 23.

SENIYA, C., YADAV, A., UCHADIA, K., KUMAR, S., SAGAR, N., SHRIVASTAVA, P. *et al.* (2012) Molecular docking of (5E)-3-(2-aminoethyl)-5-(2-thienylmethylene)-1, 3-thiazolidine-2, 4-dione onHIV-1 reverse transcriptase: Novel drug acting on enzyme, *Bioinformation*, 8(14): 678–683. https://doi.org/10.6026/97320630008678

SHEHU, I. A., MUSA, M. K., ALOK, S. & VERMA, A. (2021) Clinical features, treatment approaches and promising contributions of nanomedicines towards COVID-19, *International Journal of Pharmaceutical Sciences and Research*, 12(4): 1958–1965.

SHI, J., AISAKI, K., IKAWA, Y. & WAKE, K. (1998) Evidence of hepatocyte apoptosis in rat liver after the administration of carbon tetrachloride, *American Journal of Pathology*, 153(2): 515–525. https://doi.org/10.1016/S0002-9440(10)65594-0

SHIN, E. M., ZHOU, H. Y., GUO, L. Y., KIM, J. A., LEE, S. H., MERFORT, I. *et al.* (2008) Anti-inflammatory effects of glycyrol isolated from *Glycyrrhiza uralensis* in LPS-stimulated RAW264.7 macrophages, *International Immunopharmacology*, 8(11): 1524–1532. https://doi.org/10.1016/j.intimp.2008.06.008

SIMONE, F. D., AQUINO, R., TOMMASI, N. D., MAHMOOD, N., PIACENTE, S. & PIZZA, C. (2001) Anti-HIV aromatic compounds from higher plants, IN: C. TRINGALI (Ed.). *Bioactive compounds from natural sources*, p 305 (London: Taylor and Francis)

SINHA, S. K., PRASAD, S. K., ISLAM, M. A., GURAV, S. S., PATIL, R. B., ALFARIS, N. A. *et al.* (2020) Identification of bioactive compounds from *Glycyrrhiza glabra* as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: A pharmacoinformatics study, *Journal of Biomolecular Structure and Dynamics*, 39(13): 4686–4700. https://doi.org/10.1080/07391102.2020.1779132

TANAKA, Y., KIKUZAKI, H., FUKUDA, S. & NAKATANI, N. (2001) Antibacterial compounds of licorice against upper airway respiratory tract pathogens, *Journal of Nutritional Science and Vitaminology*, 47(3): 270–273. https://doi.org/10.3177/jnsv.47.270

TAN, R., XIANG, X., CHEN, W., YANG, Z., HU, W., QU, H. *et al*. (2022) Efficacy of diammonium glycyrrhizinate combined with vitamin C for treating hospitalized COVID-19 patients: A retrospective, observational study, *An International Journal of Medicine*, 115(2): 77–83. https://doi.org/10.1093/qjmed/hcab184

TSAY, H. S., SHYUR, L. F., AGRAWAL, D. C., WU Y. C. & WANG, S. Y. (2016) *Medicinal plants—Recent advances in research and development* (Springer Singapore). https://doi.org/10.1007/978-981-10-1085-9

VAN DE SAND, L., BORMANN, M., ALT, M., SCHIPPER, L., HEILINGLOH, C. S., STEINMANN, E. *et al.* (2021) Glycyrrhizin effectively neutralizes SARS-CoV-2 *in vitro* by inhibiting the viral main protease, *Viruses,*13(4): 609. https://doi.org/10.3390/v13040609

VARDHAN, S. & SAHOO, S. K. (2020) *In silico* ADMET and molecular docking study on searching potential inhibitors from limonoids and triterpenoids for COVID-19, *Computers in Biology and Medicine*, 124: 103936. https://doi.org/10.1016/j.compbiomed.2020.103936

VIKHE, G. P., VIKHE, P. P., NAIK, S. S., GAVHANE, A. J. & GAIKAR, R. B. (2013) *In vitro* effect of *G. glabra* and *T. cordifolia* plant extracts on phagocytosis by human neutrophils, *Pravara Medical Review*, 5(2): 12–15.

WANG, X. Q., LI, H. Y., LIU, X. Y., ZHANG, F. M., LI, X., PIAO, Y. A. *et al*. (2006) The anti-respiratory syncytial virus effect of active compound of Glycyrrhiza GD4 *in vitro*, *Zhong Yao Cai*, 29(7): 692–694. Chinese.

WANG, Z., LUO, S., WAN, Z., CHEN, C., ZHANG, X., LI, B. *et al*. (2016) Glabridin arrests cell cycle and inhibits proliferation of hepatocellular carcinoma by suppressing braf/MEK signaling pathway, *Tumor Biology*, 37(5): 5837–5846. https://doi.org/10.1007/s13277-015-4177-5

YANG, R., YUAN, B. C., MA, Y. S., ZHOU, S. & LIU, Y. (2017) The anti-inflammatory activity of licorice, a widely used chinese herb, *Pharmaceutical Biology*, 55(1): 5–18. https://doi.org/10.1080/13880209.2016.1225775

YONESI, M. & REZAZADEH, A. (2020) Plants as a prospective source of natural anti-viral compounds and oral vaccines against COVID-19 coronavirus. Preprint. pp.1–23. https://doi.org/10.20944/preprints202004.0321.v1