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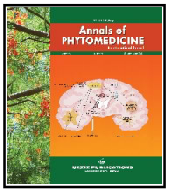

Review Article : Open Access

Scrutinizing glycyrrhizin and its derivatives in the management of respiratory disorders including SARS-CoV (COVID-19)

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Abstract

Licorice, commonly known as mulethi, is a very familiar plant for its possible antiviral activity against several RNA and DNA viruses. It restrains a variety of bioactive composites with a triterpenoid saponin, *i.e.*, glycyrrhizin or glycyrrhizic acid (GLR), obtained principally from the roots of the plant. It has been found to inhibit the replication, adsorption, and penetration of SARS-associated coronavirus into cells and is reported to have antiviral properties against influenza, herpes, hepatitis, and SARS viruses. *Glycyrrhiza glabra* L. (Licorice), family Fabaceae mainly composed of 18 beta-glycyrrhetinic acid, glabrin A, and B. Numerous studies claim that these active compounds exert antioxidant, anti-inflammatory, antibacterial, and antiviral effects against a variety of viral species. The antioxidant properties of glycyrrhizin and its analogues are due to their phenolic content, flavonoids, and isoflavones. The antiviral activities are due to glycyrrhizin and its derivatives. As it inactivated and inhibited viruses, β-chemokines and virus replication. The anti-inflammatory property is due to inhibition of HMGB1/TLR4. That resulted in the inhibition of reactive oxygen species formation. This work highlighted the possible antiviral mechanism of glycyrrhizin and its derivatives observed in progressive research. The possible system might be utilised to formulate silver nanoparticles (AgNPs) as targeted drug delivery in the form of respules for the management of chronic obstructive pulmonary disease (COPD), SARS-CoV (COVID-19), and other respiratory tract disorders.

1. Introduction

COVID-19 has resulted in a 'once-in-a-century pandemic" caused by the SARS-CoV-2 virus. It happened to a group of patients with 'pneumonia of unknown cause' in the Wuhan province of China (Khan *et al.,* 2020). Epidemiologic research had shown an ordinary link-which was the disclosure of each and every one of these pretentious patients to the Huanan Seafood Market. Analysis of samples from three of these patients suffering from pneumonia and admitted to the Wuhan Jinyintan Hospital, resulted in the isolation of the SARS-CoV-2 virus from the bronchoalveolar lavage fluid on December 30, 2019 (Zhu *et al.,* 2020). Licorice contains various bioactive compounds, including triterpenoid saponins, flavonoids, phenols, coumarins, and polysaccharides (Sinha *et al.*, 2020; Jiang *et al.,* 2020). A triterpenoid saponin, *i.e.*, glycyrrhizin or glycyrrhizic acid (GLR), which is derived mostly from the roots of the plant, has been found to inhibit the replication, adsorption, and penetration of SARS-associated coronavirus into cells and is reported to possess antiviral properties against influenza, herpes, hepatitis, and SARS viruses (Thakur *et al.,* 2004). The SARS-CoV-2 virus enters the host *via* inoculation and makes an effort to establish itself in the mass. The respiratory tract is the primary target of the SARS-CoV-2 virus, and it has a high affinity for the angiotensin-converting enzyme type 2 (ACE2) receptors on the alveolar epithelial cells of the lung. The virus uses the S1 subunit of the S protein to attach to the host cell surface and then uses the S2 subunit to combine with the cell membrane of the pretentious cell. Once inside the cell, the virus goes through the next phase, in which the RNA of SARS-CoV-2 crosses the threshold, followed by the nucleus, and starts replication. Viral proteins are prepared, and fresh virions are released. The privileged transmissibility of the SARS-CoV-2 virus compared to the SARS-CoV virus can be explained by its augmented affinity for binding to the ACE2 receptor. ACE2 gene expression differs across populations because of gene polymorphisms and is probable the rationale for discrepancy vulnerability to SARS-CoV-2 infection and a number of the geographical differences in brutality of COVID-19 (Figure 1) (Khan *et al.,* 2020).

The name 'Glycyrrhiza' comes from two Greek expressions: 'glykos' (sweet) and 'rhiza' (root). Consequently, glycyrrhiza is usually recognised as Licorice or sweet wood. Many glycyrrhiza species are used as anticancer, antibacterial, antifungal, antiallergic, asthma, anti-inflammatory, antioxidant, hepatoprotective, cardioprotective, neuroprotective, antialzheimer's, antidepressant, hypnotic, antiulcer, antitussive, expectorant, antithrombotic, antiosteoporotic, *etc.,* activities (Banerjee *et al.,* 2023).

The compounds taken from glycyrrhiza species also have a spacious series of antiviral efficacies next to diverse viruses, for instance, hepatitis, dengue (Baba and Shigeta, 1987), influenza, HIV, porcine reproductive and respiratory syndrome virus (Curreli *et al.,* 2005), coxsackie A16 and entero, rota, duck hepatitis, human respiratory

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syncytial, epstein-Barr, human papilloma, bovine viral diarrhoea, porcine epidemic diarrhoea, varicella-zoster, herpes (Fiore *et al.,* 2008), and SARS-CoV viruses (Huang *et al.,* 2020). Researchers and people engaged in healthcare are doing remarkable work now to recognise various approaches for COVID-19 management (Jadhav and Mehrotra, 2022).

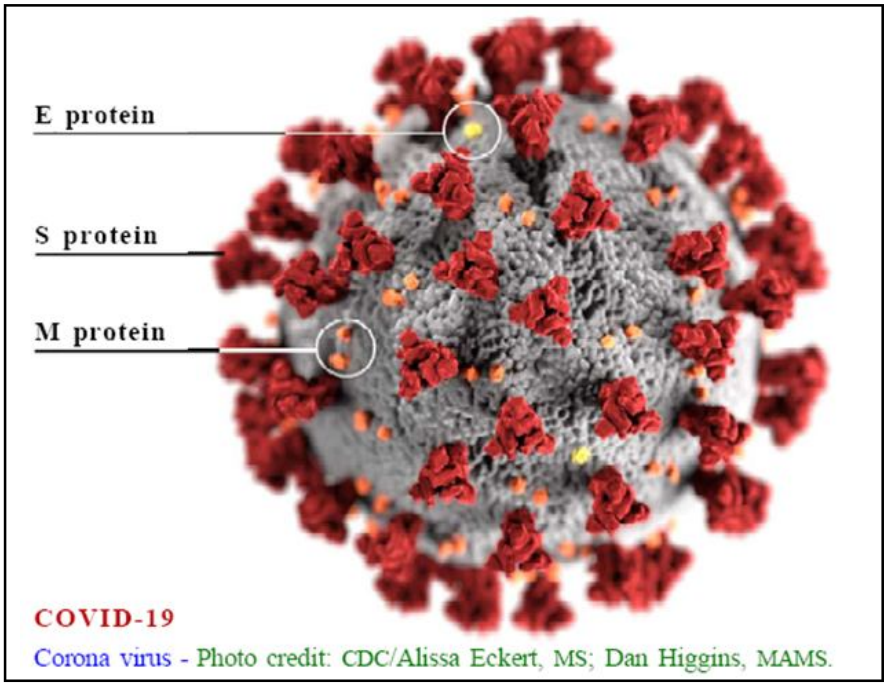

Figure 1: Structure of corona virus.

COVID-19 primarily affects the lungs; several clinical consequences have been observed, like cardiac damage, thromboembolic events, arrhythmia, and immunological dysregulation (Wahab *et al.,* 2021). Liquorice is an herbaceous perennial legume native to Western Asia, Southern Europe, and North Africa (Ashfaq *et al.,* 2011). The root extract of liquorice has been used in traditional Indian medicines and several ayurvedic preparations (Bradley *et al.,* 2014; Cinatel *et al.,* 2003). It has been glowingly recognised in prehistoric remedial volumes of India, China, and Greece and has been consumed in herbal formulations for thousands of years (Ding *et al.,* 2020; Michaelis *et al.,* 2011; Yu *et al.,* 2021). Liquorice was prescribed for the prevention and cure of various diseases like indigestion, respiratory diseases, and immune system related issues. Today, a lot of experimental evidence is available that supports its favourable antibacterial, antiviral, antioxidant, anticancer, antihypertensive, hypoglycemic, liver protective, and neuroprotective properties (Zeng *et al.,* 1988). Glycyrrhizin and glycyrrhetinic acid are the major phytoconstituents obtained from the root extract of liquorice, which belongs to the class of triterpenoids. Through the G.I.T., glycyrrhizin is metabolised into glycyrrhetinic acid (Figure 2). (Van *et al.,* 2021)

Plants acted as both the primary food source and the source of medicine. A comprehensive perspective on the pathways of secondary metabolism in plants and their conservation status, ecology, and ethnobotany is an important key for drug development. It is a centre of attention as medicinal plants generate numerous significant chemical compounds throughout their secondary metabolism, functioning as self-defence in opposition to stress induced by environmental triggers and pathogens. From using the raw plant to extracting important compounds, medicinal plants are centuries-old sources in the various traditional herbal medicine systems. For instance, their importance lies in the fact that the WHO concludes that 80% of the world's population relies on them for treatment.

Glycyrrhizin, also called glycyrrhizic acid (GLR), is a triterpenoid saponin mainly isolated from the roots (*glycyrrhizae radix*) of the plants *G. glabra* (typically cultivated in Europe, henceforth called European Licorice) and *Glycyrrhiza uralensis* Fisch. and *Glycyrrhiza inflata* Bat. (used in the Chinese Pharmacopoeia) (Pastorino *et al.,* 2018; Hayashi *et al.,* 2019; Wang, Chen *et al.,* 2020). *G. glabra* contains more than 10 GLR-related saponins (Schmid *et al*., 2018). The product has also been found in other Glycyrrhiza species, such as *Glycyrrhiza triphylla* (Shakeri *et al.,* 2018), and in an edible marine alga, *Hizikia fusiformis* (harvey) Okamura, brown seaweed (Seong *et al.,* 2019; Wagle *et al.,* 2018). GLR is commonly isolated from *Glycyrrhizae radix* in the form of a monoammonium salt ($C_{42}H_{61}O_{16}NH_4$), but occasionally studies are performed with the magnesium salt of 18 β-glycyrrhizic acid (magnesium isoglycyrrhizinate) (Bailly *et al.,* 2020; Tan *et al.,* 2021). A specific methods have been developed to monitor the extraction process and dosages in biological media (Wang, Chen *et al.,* 2020).

Since Licorice has glycyrrhizin and other constituents. There is an increase in attention to the precise method of using glycyrrhizin in COVID-19. In the present compilation, we have focused on the chemistry, pharmacology, and antiviral properties of glycyrrhizin and its potential use for the treatment of coronavirus infections. The article further highlighted the pathway for advanced research and formulation development of glycyrrhizin.

2. Chemistry

Glycyrrhizin (Figure 2), a triterpenoid compound, accounts for the sweet taste of Licorice root. It is a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2-25% range. Among the natural saponins, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhetic acid (Figure 2) (Sharma *et al.,* 2018).

GLR is a glycoside of glycyrrhetinic acid (GA, the sapogenin moiety) with two residues of glucuronic acid (Figure 2). GA is the major metabolite of GLR, together with 3-O-mono-β-D-glucuronyl-glycyrrhetinic acid (3MGA) and a minor sulfated metabolite (Bailly *et al.,* 2020; Morinaga *et al.,* 2018). Orally administered GLR is metabolised into GA by intestinal bacteria and absorbed *via* the intestine. Nevertheless, GLR is detected in human plasma after oral administration of a clinical dose of GLR (Suzuki *et al.,* 2017). Both oral and intravenous formulations of GLR are used in humans.

The natural product exists as two epimers, 18 α-glycyrrhizic acid (18 α-GLR) and 18 β-glycyrrhizic acid (18 β-GLR), both active, although the 18 β-isomer seems to be more potent than the 18 α-isomer. Indeed, 18 β-glycyrrhetinic acid (IC_{50} = 8.9 μM) was found to be about 2-fold more active than GLR (IC_{50} value of 20.1 μM) and 11-fold more potent than 18 α-glycyrrhetinic acid (IC_{50} = 104.3 μM) in an enzyme BACE1 inhibition assay (butyrylcholinesterase and β-site amyloid precursor protein cleaving enzyme 1) (Wagle *et al.,* 2018). Bioproduction methods using metabolically engineered *Saccharomyces cerevisiae* (yeast cell factories) are being developed as an alternative "greener" approach to producing GLR (Wang *et al.,* 2019). β-glucuronidase enzymes can be used to biotransform GLR into GA (Bailly *et al.,* 2020). The product is often used as a natural emulsifier and gel-forming agent in foodstuffs, beverages, and cosmetics. GLR has been approved for use as an additive in foods since 1985 in the US and has a Generally Recognised as Safe (GRAS) status.

3. Pharmacology

In biology and medicine, GLR has been extensively studied for its very diverse pharmacological properties, including anti-inflammatory, antioxidative, antiallergenic, antimicrobial, antiviral, antiparasite, and anticancer properties. The properties and applications of GLR and GLR-containing extracts have been reviewed previously (Chen *et al.,* 2019; El-Saber Batiha *et al.,* 2020; Kwon *et al.,* 2020; Ming *et al.,* 2013). Glycyrrhizin also showed many pharmacological effects and potential inhibitory effects against influenza virus, severe acute respiratory syndrome associated with COVID-19 (Ding *et al.,* 2020), herpes simplex type 1 (Hirabayashi *et al.,* 1991), and hepatitis C virus (Zeng *et al.,* 1988).

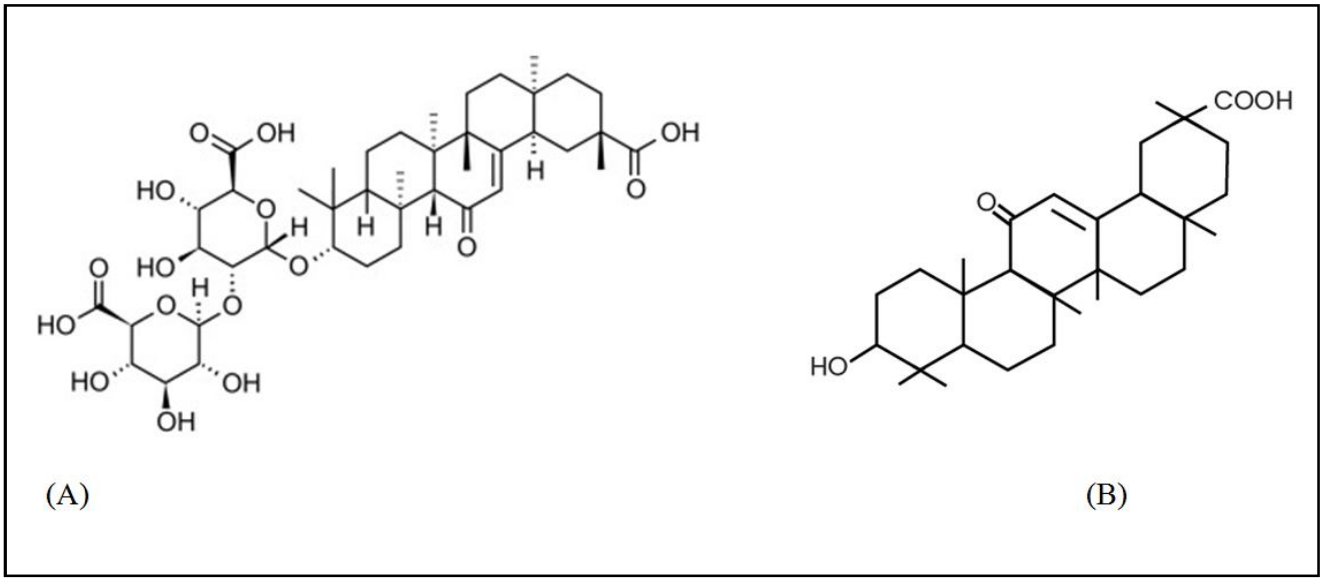

Figure 2: The chemical structure of glycyrrhizinic acid (A) and glycyrrhetinic acid (B).

The USFDA, WHO, and Council of Europe have allowed the use of glycyrrhizin and its derivatives in food and nutritional products. Natural plant-based medicines are also now approved for and in use in many countries in Africa, along with countries like India, China, and Brazil. These products have anti-inflammatory, antiviral, and immunomodulatory properties, which may help in initial protection from the virus. There are thousands of medicinal plants available in nature that would show many health benefits, and among them are some important Indian plants recommended by AYUSH. Glycyrrhiza species are also suggested for their valuable active constituents (Khan *et al.,* 2020). In the Indian system of medicine, liquorice was frequently used as an herbal medicine for the treatment of several disorders of the respiratory tract, digestive system, circulatory system, *etc.* without any side effects. (Gowda *et al.,* 2021).

4. Activity against influenza virus

Glycyrrhizic acid inhibits the replication of influenza virus in chicken embryos by reducing haemagglutinin levels (Okonko and Cookey, 2015). It has also been reported through *in vitro* studies (Lu *et al.,* 2003; Pu *et al.,* 2013), the mechanism of inhibitory properties of influenza virus replication by glycyrrhizic acid. Influenza virus combines with HMGB1 which promotes the activity of virus polymerase and the growth of influenza virus (Michaelis *et al.,* 2011).

Glycyrrhizin causes the inhibition of influenza virus replication by reducing the activity of influenza virus polymerase through antagonising the binding effect (Lu *et al.,* 2003). Glycyrrhizin (200 ìg/ml) significantly inhibits the cytopathic effect caused by influenza A virus (H5N1) infection at an MOI of 0.01, 0.1, and 1, respectively, in A549 cells (Reward *et al.,* 2019). Glycyrrhizin directly hinders the replication of the extremely pathogenic H5N1 at curative concentration induces the formation of reactive oxygen species (ROS) by H5N1, resulting in the reduction of p38 activation, NF-kB, and JNK in lung cells. Inhibition of H5N1 induces the production of CXCL10, CCL5 (MOI 2), and IL-6, as was also found by glycyrrhizin. Glycyrrhizin was also found to inhibit H5N1, provoke apoptosis without affecting virus reproduction and NK cell activity (Lu *et al.,* 2003). A combination of glycyrrhizin or glycyrrhizic acid with other drugs shows antagonistic effects against the influenza virus. The studies performed on the regulatory effects of glutamyl-tryptophan and glycyrrhizic acid and their combination on influenza A H3N2 virus infection in mice at 1 or 10 LD50 (Michaelis *et al.,* 2010). The studies revealed and concluded that glutamyl tryptophan alone, glycyrrhizic acid at 10 mg/kg body weight in combination with glutamyl tryptophan (0.1 µg/kg, 10 µg/kg, and 1,000 µg/kg) show significant effects as antivirals and proved best for the management of lung oedema and inflammatory cell infiltration. A combination of the antiviral drug ribavirin with glycyrrhizic acid has a synergistic effect and significantly inhibits lung consolidation in mice infected with the H1N1 influenza virus (Table 1).

Table 1: Antiviral effects of glycyrrhizin and its derivatives (Sakai-Sugino *et al.,* 2017)

Glycyrrhizin and its derivatives	Mechanism of action	Virus	References
Glycyrrhizin (50 µg/ml, 100 µg/ml, 200 µg/ml)	Inhibits H5N1-induced CXCL10, IL-6 and CCL5 production, inhibits H5N1-induced apoptosis but does not interfere with H5N1 replication	H5N1	Reward *et al.,* 2019
Glycyrrhizin (25 µg/ml, 50 µg/ml, 100 µg/ml, 200 µg/ml)	Inhibits the formation of ROS induced by H5N1 and then decreases the activation of NFêB, JNK, and p38	H5N1	Michaelis *et al.,* 2011
Glycyrrhizin (after virus adsorption, EC50 600 µg/ml; during and after virus adsorption, EC50 300 µg/ml; during virus adsorption, EC50 2,400 µg/ml)	Inhibits virus replication; inhibits the adsorption and infiltration of viruses	SARS-CoV	Cinatel *et al.,* 2003
Glycyrrhizin (10 mM, 250 mM, 1,000 µM)	Inhibition of HMGB1 release; inhibition of virus replication	SARS-CoV-2	Gowda *et al.,* 2021
Glycyrrhizic acid (8 mM)	Directly inactivates herpes simplex virus	HSV-1	Huan *et al.,* 2017
Carbenoxolone sodium (500 µM) and cicloxolone sodium (300 µM	Inhibition of virus replication	HSV-1, HSV-2	Pompei *et al.,*1983
Glycyrrhizin (0.5 mg/ml, 1 mg/ml, 2 mg/ml)	Inhibition of hepatitis B surface antigen secretion, sialylation, and intracellular transport	HBV	Dargan *et al.,* 1986
Glycyrrhizin (2.5 µg/ml, 5 µg/ml, 10 µg/ml, 20 µg/ml)	Inhibition of HCV3a core gene expression at mRNA and protein levels	HCV	Ashfaq *et al.,* 2011
Glycyrrhizin (0.075, 0.15, 0.3, 0.6, 1.2, 2.4 mM)	Inhibition of virus replication by inhibiting protein kinase C	HIV-1	Takahara *et al.,* 1994
Glycyrrhizin (0.06 mg/ml, 0.13 mg/ml, 0.25 mg/ml, 0.5 mg/ml, 1 mg/ml)	Reduces the fluidity of cell membrane, resulting in a decrease in intercellular fusion, thus inhibiting the transmission of HIV between cells	HIV-1	Ito *et al.,* 1988

5. Activity against SARS-CoV

The evaluation of the antiviral effects of ribavirin and glycyrrhizin against SARS-CoV infection was performed, and it was concluded that glycyrrhizin exhibited the strongest inhibitory effect on SARS-CoV replication in vero cells (Cinatel *et al.,* 2003; Baruah *et al.,* 2021). A study explained the inhibition of the early stages of the virus replication cycle, adsorption, and penetration by glycyrrhizin. The effect of glycyrrhizin addition on SARS-CoV was not found to be as good as that of glycyrrhizin addition after virus adsorption. The results of clinical trials revealed that clinical symptoms like dyspnea were managed quickly, the average time for lung lesion improvement from the most severe 50% decreased (Sakai-Sugino *et al.,* 2017), and almost no side effects were observed in the group during the treatment of infection with glycyrrhizin (Harada, 2005). The homology in gene sequence between SARS-CoV-2 and SARS-CoV is about 79.5% (Yang, 2020), and many common clinical symptoms have been observed in the infection caused by these two viruses (Zhou and Huang, 2019). A study performed by Luo *et al.* (2020) explored the therapeutic effects of glycyrrhizin in the clinical management of COVID-19. After a detailed review of the literature, it was found that glycyrrhizin shows significant effects against SARS-CoV and SARS-CoV-2 and exerts various therapeutic and pharmacologic effects such as ACE2 binding, endogenous interferon induction, proinflammatory cytokine downregulation, inhibition of intracellular R accumulation and thrombin, and excessive production of exudates in the airways. These studies suggest that glycyrrhizin may prove a promising drug against viral infections, especially in the management

of airway passage and respiratory infections (Ding *et al.,* 2020). Gowda *et al.* (2021), and Husain (2021), explained the significant inhibitory effect of glycyrrhizin against SARS-CoV-2 (MOI 0.01) replication in Vero E6 cells in a dose dependent manner with no significant toxic effect. It also inhibits viral replication through the viral main protease (Yu *et al.,* 2020). The computer-advanced drug design and biological verification declared that glycyrrhizin is the best therapeutic agent with a nontoxic broad spectrum antiviral drug *in vitro*, particularly against COVID-19 or SARS-CoV-2. Some investigations suggest that glycyrrhizin may also have beneficial effects with beta-2 bronchodilators, *i.e.*, albuterol, in patients suffering from COPD (Tandon *et al.,* 2001). *G. glabra* was used with other drugs in Ayurveda and Unani formulations to enhance immunity against SARS-CoV-2 (Alam and Khan, 2022).

6. Activity against other viruses

A study revealed that glycyrrhizic acid could directly inactivate the Herpes simplex virus, which is an irreversible effect (Okonko and Cookey, 2015). Glycyrrhetinic acid and its derivatives, carbenoxolone sodium and cicloxolone sodium, have anti-HSV properties (Pompei *et al.,* 1983). Hirabayashi *et al.* (1991) found that carbenoxolone sodium 500 µM and cicloxolone sodium 300 µM had anti-HSV-1 and anti-HSV-2 activities during *in vitro* and *in vivo* studies. It may reduce virus replication considerably and the quantity of infectious virus particles by 10,000-100,000 times. HSV-1 replication is reduced by glycyrrhizin and glycyrrhetic acid. However, glycyrrhetic acid showed 10 times superiority as evaluated in the midst of glycyrrhizin (Gowda *et al.,* 2021). Glycyrrhizin was also having an effect on reducing the adhesion between polymorphonuclear leucocytes and cerebral capillary vessel endothelial cells in the treatment of Herpes simplex virus infection (Hirabayashi *et al.,* 1991). Glycyrrhizic acid exerts activity against the hepatitis virus with low toxicity in host cells. It is commonly used for the treatment of chronic hepatitis and can restrain the discharge of HBV surface antigen in PLC/PRF/5 cells *in vitro*. Glycyrrhizin binds to hepatocytes at a certain concentration, changes the expression of HBV related antigen on hepatocytes, and reduces sialylation at a certain concentration (Harada, 2005). In combination with lamivudine, glycyrrhizin may inhibit the replication of HBV in an HBV carrier with non-Hodgkin lymphoma. Glycyrrhizin completely inhibits HIV induced (MOI 0.002) MT-4 cell plaque formation and also HIV induced cytopathogenicity in MT-4 and MOLT-4 cells *in vitro* at a concentration of 0.6 mM (Hirabayashi *et al.,* 1991). The antimicrobial mechanism of glycyrrhizin is elaborated in Figure 3 (Sakai-Sugino *et al.,* 2017).

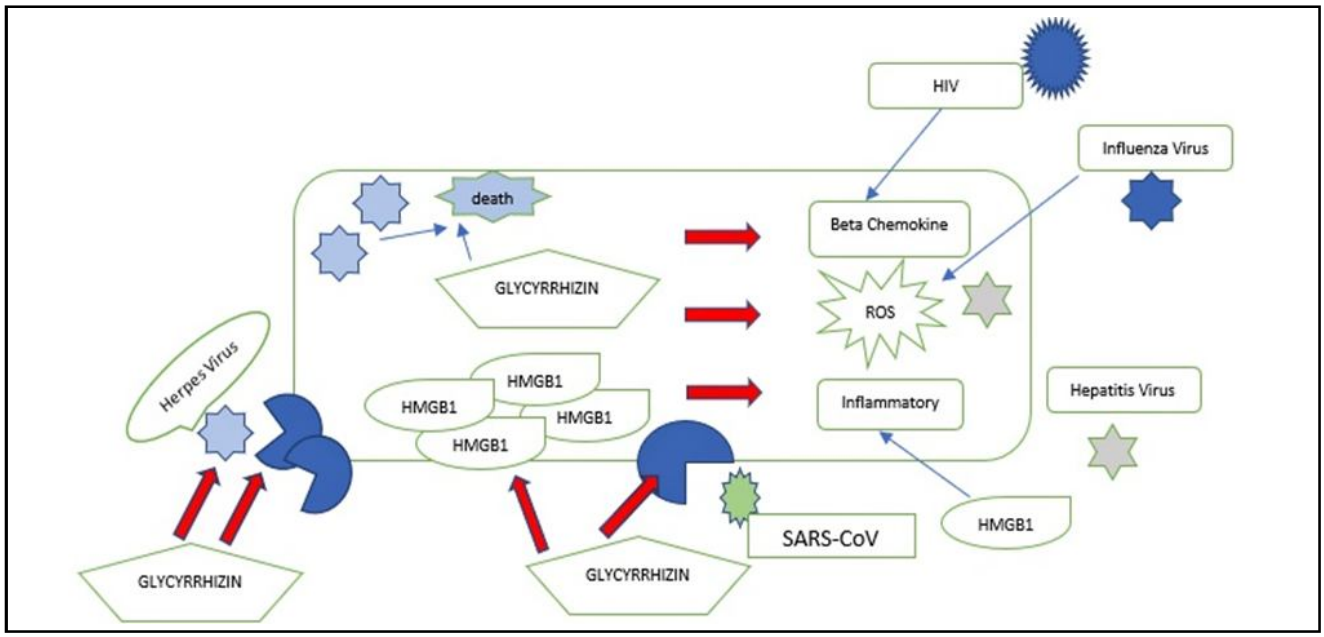

Figure 3: Antiviral mechanism of licorice root extract containing glycyrrhizin and other derivatives. Activation (⇨), inhibition (➡), HMB1= High mobility group box 1, ROS = Reactive oxygen species, HIV = Human immunodeficiency virus.

7. Discussion

In formulation development, one of the targets for wide spectrum anti SARS-CoV-2 is RNA-dependent RNA polymerase (Mpro, a non-structural protein). Ethanolic extracts of *Glycyrrhiza radix* demonstrated anti-SARS-CoV-2 activity. The glycyrrhizin and its metabolites effectively bind to Mpro (Shamna *et al.,* 2022). The proficient binding capability of glycyrrhizic acid at the boundary of the spike protein receptor-binding domain (RBD) and the human ACE2 receptor makes it an effective inhibitor of the virus (Sumathi and Vidhya, 2022). Exploiting the promising therapeutic potential of plant phytoconstituents to combat COVID-19: A review The expectations of drug development from medicinal plants can economically facilitate the management of prevention and alleviation of COVID-19 disease. Mulethi (*Glycyrrhizin gabra* L.) is one of the Ayurvedic rasayanas used during COVID-19 (Khushi and Sarla, 2022). To enhance the immune system and fight against COVID-19, the Ministry of Ayush, Government of India, has published guidelines that include the preparation of kadha and turmeric milk and spices and herbs (pudina, ajwain, and clove powder) that are present in the kitchen and have been proven to be beneficial in the treatment of

respiratory infections. The current study emphasises on which spices, herbs, and other supplements were used during COVID-19 and which helped people survive the pandemic situation (Ministry of Ayush, 2020).

8. Conclusion

Glycyrrhizin and its derivatives act as antiviral *via* the inhibition of virus replication. It is directly involved in the inactivation of viruses, hang-up the replication and appearance of viral genes, responsible for cell death enhancement. The inhibition of β-chemokines, decreased inflammation caused by HMGB1/TLR4, declined HMGB1 release and its binding. Further weakened the DNA of viruses, fluidity of the cell membrane reduced, and the formation of the ROS inhibited. Many more mechanism may further be discovered which further help to develop a best antiviral remedy from this herbal drug. This work may help to design a suitable dosage form for the clinical management of severe, chronic and acute viral infections related to COPD.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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