

Review Article

Study on Antiviral Activities of Glycyrrhizin

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Abstract: Licorice has been a common Chinese medicine for thousands of years, which has good medicinal value and nutritional value. It widely applies to traditional Chinese medicine. Many studies have shown that licorice contains more than 20 triterpenoids and nearly 300 flavonoids. According to the literature, licorice has many activities such as antibacterial, antiviral, antioxidant, and anticancer. It not only directly inactivates the virus, but also inhibits its adsorption. However, glycyrrhizin, glycyrrhetic acid, glycyrrhiza polysaccharide and glycyrrhiza flavonoids are the main components of licorice which possess antiviral and antimicrobial activities. Among them, glycyrrhizin has many pharmacological activities, such as antiviral, anti-inflammatory, anti-tumor, antibacterial and many other activities. This paper provides a summary of antiviral activities of glycyrrhizin. This active ingredients and possible mechanisms are summarized in detail. The results showed that glycyrrhizin was widely used in antiviral field, but its material basis and mechanism of action were not perfect and unified. A large number of literatures about glycyrrhizin anti-virus were reviewed and analyzed, and it was suggested that more different ways should be adopted to study it, so as to provide a broader theoretical basis for developing new antiviral drugs of glycyrrhizin. It is hoped that this review will be helpful to further study the potential therapeutic effect of glycyrrhizin as an antiviral drug.

Keywords: Glycyrrhizin, Antiviral, Chinese Medicine

1. Introduction

Glycyrrhizin (GL) is a triterpenoid saponin, one of the main compounds isolated from the roots of licorice. GL contains one molecule of glycyrrhe-tiic acid, with structural similarities to hydrocortisone, and two molecules of glucuronic acid. GL has been shown that several beneficial pharmacological activities, including anti-inflammatory activity [1], anti-tumor activity [2], anti-allergic activities [3], and antiviral activities [4]. In recent years, there have been more and more research reports on the antiviral activity of GL, such as hepatitis C virus (HCV), human immunodeficiency virus (HIV), duck hepatitis Virus (DHV), severe acute respiratory syndrome coronavirus

(SARS-COV) and so on.

2. Antiviral Activities of GL and Possible Mechanisms

2.1. HCV

Ashfaq et al. reported that at the concentration of 14.2 µg/ml, GL inhibited the titer of hepatitis C virus by inhibiting the expression of full-length virus particles and its core genes, and reduced hepatitis C virus by 50% [5]. At 40µg/ml concentration, viral inhibition of GL reached up to 89%. And Matsumoto et al. reported that GL inhibits the release of

hepatitis C virus, but not assembly and budding [5].

2.2. HIV

GL can induce interferon, enhance the function of NK cells and inhibit HIV replication. According to Takei *et al.* [6], GL can inhibit the infection of R5 HIV virus and the expression of CCL2 or IL-10 coreceptor CCR5. And GL inhibits the production of CCL2/IL-10 by polymorphonuclear neutrophils (PMN) stimulated by R5 HIV and inhibits the PMN-dependent increase of R5-HIV replication in monocyte-derived macrophages (MDMs) [7].

2.3. PEDV

Huan *et al.* reported that porcine epidemic diarrhea virus (PEDV) infection caused release of high mobility group box-1 (HMGB1), and that the HMGB1 competitive inhibitor GL inhibits PEDV infection and attenuated proinflammatory responses [8]. GL prevents binding HMGB1 to toll-like receptor 4 (TLR4) to inhibit PEDV infection, and this effect depends on the HMGB1/TLR4-MAPK p38 pathway [9].

2.4. PRRSV

According to Duan *et al.* [10], GL is also effective against the porcine reproductive and respiratory syndrome virus (PRRSV, an enveloped single positive-strand RNA virus, Arterivirus), and their results showed that GL significantly reduced PRRSV proliferation and PRRSV-encoded protein expression in a dose-dependent manner.

2.5. HSV

Herpes simplex virus (HSV) is a neurotropic DNA virus, which can induce a variety of diseases including infection of central nervous system, mucocutaneous infections and occasionally infections of visceral organs. According to some reported studies, GL can inhibit adhesion between PMN and cerebral capillary vessel endothelial cells (CCEC) and thus playing a beneficial therapeutic role during HSV infection [11].

2.6. H5N1

GL inhibits the replication of highly pathogenic H5N1 influenza A virus, apoptosis induced by H5N1, and H5N1-induced expression of pro-inflammatory cytokines CXCL10, IL-6, CCL2, and CCL5 in lung-derived A549 cells. GL does not affect the expression of cytokines in uninfected cells, but inhibited the expression of all cytokines studied in H5N1 infected cells in a dose-dependent manner [12, 13]. Moreover, activation of NF- κ B, MAPKs p38, and JNK has been associated with influenza A virus replication and virus-induced pro-inflammatory gene expression [14-16].

2.7. SARS-CoV

In addition to inhibition virus replication, GL inhibits adsorption and penetration of the virus at the early stage of replication cycle. The effect of adding GL during adsorption is not as good as adding after virus adsorption (EC₅₀ 600

mg/L vs 2400 mg/L, respectively). GL is most effective when given both during and after the adsorption period (EC₅₀ 300 mg/L) [17]. Through the introduction of certain chemical modifications, it is proved that it is possible to increase the antiviral efficacy of GL. but as these modifications also increase the cytotoxicity. The selectivity index of GL derivatives is reduced as compared with that of GL (selectivity index: ≥ 65) [18].

3. Recent Advances in Antiviral Activity of Glycyrrhizin

SARS-CoV-2 (COVID-19)

The recent pandemic 2019 novel coronavirus, also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [19]. It has been found that the severity of SARS-CoV-2 infection ranges from asymptomatic to mild respiratory infections, and then to severe to fatal pneumonia. At present, there is no vaccine or specific treatment for this novel virus. Therefore, it is urgent to put forward new treatment interventions for COVID-19.

Some studies have shown that reducing angiotensin converting enzyme 2 (ACE2) expression can reduce the number of access points of the virus to the body during the primary infection and potentially the spread inside the body [20]. GL is metabolized in the human body into glycyrrhetic acid (GA). GA primarily inhibits an enzyme called 11-beta-hydroxysteroid dehydrogenase (11bHSD), both type 1 and 2. 11bHSD2 is an inhibition of this enzyme leads to an aldosterone like activation of MR via cortisol and may resemble the effects of high aldosterone levels in these organs. Interesting, high aldosterone levels lead to a down-regulation of ACE2 in the kidney [21]. Moreover, recent studies have shown that GL has the potential to bind directly to ACE2 and affect the expression of ACE2. GL may still be considered as a potential treatment for COVID-19 as it has an antiviral effect on SARS-CoV (ACE2 is also a functional receptor for the SARS-CoV) [22].

4. Discussion and Conclusion

Presently we have summarized the antiviral activities of GL. Many studies reveal that GL is responsible for the antiviral activities through different mechanisms. Antiviral effects of GL on early steps in the viral lifecycle, for example the inhibition of endocytosis of influenza A virus, the direct fusion of HIV, the virus entry and replication of SARS and PEDV. Then, GL inhibits HCV full length viral particle and HCV core gene expression both at RNA and protein level and has synergistic effect with interferon. GL can be used as an immunomodulatory agent against virus infection since GL treatment attenuates the production of some cytokines. GL may be capable to reduce the expression of ACE2 in the lung and lung inflammation, relieve lung symptoms, so it is helpful to treat respiratory diseases.

At present, the COVID-19 is still serious. We hope this

study be helpful to the research of GL treating COVID-19.

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