

FULL PAPER

Prospects for the development of drugs with anti-viral activity based on licorice

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The current situation with the widespread of a socially dangerous virus from the genus Coronavirus (SARS-CoV-2) and the announcement of a pandemic in connection with this demand the creation of new antiviral drugs since no specific treatment and prophylaxis against this disease has yet been found. Among medicinal plants that are widespread and exhibit multidirectional pharmacological activity, licorice should be noted. The active components contained in licorice, i.e. more than 20 triterpenoids and about 300 flavonoids coupled with glycyrrhizic acid (GL) referred to by the term "glycyrrhizin", have been widely studied for a long time. GL acts indirectly, interferes with the penetration of the virus into the cell, affects the components (HMGB1 protein) necessary for normal viral reproduction, and potentiates the production of interferon γ and α . GL acts against SARS-associated coronavirus infection by inducing the synthesis of nitric oxide synthase, which inhibits viral replication. However, GL may also be helpful in acute respiratory distress syndrome. The combination of the multidirectional pharmacological effects of GL and its derivatives make the licorice-containing preparations promising components of complex antiviral therapy. Currently, research into licorice-containing dosage forms continues from the perspective of creating vaginal suppositories with a thick extract of licorice

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Introduction

The development of effective therapeutics against various diseases including coronavirus disease remains one of the most important tasks of medicinal chemistry and pharmacy [1]. The current situation with the widespread of a socially dangerous virus from the genus Coronavirus (SARS-CoV-2-an enveloped virus) and the announcement of a pandemic in this regard requires the creation of new antiviral drugs since specific antiviral agents for the treatment or prevention of this disease, having not found yet [2-5]. In the

development of the pathological process caused by coronaviruses, two early and late stages can be distinguished. At the early stage, when the virus accumulates, agents have prescribed that block the multiplication of coronaviruses. Chemotherapeutic approaches at this stage are aimed at various targets in the replication of coronaviruses and include inhibitors of viral RNA polymerase, inhibitors of the viral protease (Mpro), inhibitors of proteolytic activation of viral protein S, which enters the target cell, inhibitors of viral deproteinization in cell endosomes, and exogenous interferon preparations,

preparations of natural and recombinant virus-neutralizing antibodies, as well as combinations of the above preparations. At the second stage, pathogenetic stage, when the multiplication of the virus falls and threatening pathological processes begin to dominate, i.e. excessive inflammation, acute respiratory distress syndrome, pulmonary tissue edema, hypoxia, threatening sepsis, it is recommended to use extracorporeal blood oxygenation and prescribe detoxifying, anti-inflammatory and antibacterial therapeutic agents [2]. Therefore, to prevent the development of severe pathogenetic consequences of COVID-19, it is necessary to stop the disease at the first, early stage. Therefore, research on the proposal of new antiviral drugs is so relevant.

The antiviral drugs currently available in the array of pharmacotherapy are compounds of natural or synthetic origin, the action of which is aimed either at stimulating the immune system or at disrupting various stages of the development of viral infection or the life cycle of viruses, the process of virus adsorption on the cell membrane, penetration into the cellular cytoplasm, intracellular synthesis of viral components, assembly of viruses, release of daughter virions from the host cell [3]. Various modern medicines are synthesized based on chemical compounds of plant origin. Many years of experience in using medicinal plants in folk medicine, the chemical diversity of their components, availability, and most importantly, naturalness make herbal components a priority component of modern production and pharmacotherapeutic techniques [4].

The pharmacological effect of licorice

Among the medicinal plants that have long been used by humans, which are widespread and have a rich documented pharmacotherapeutic history, licorice (*Glycyrrhiza glabra* L.) should be noted.

The main pharmacological component of licorice roots (*Glycyrrhiza glabra* L.) and Ural (*Gl. Uralensis* Fisher) is glycyrrhizic acid (GL), a compound consisting of aglycone, represented by a triterpene derivative of glycyrrhizic acid (GLR) and a disaccharide fragment. Generally, licorice contains over 20 triterpenoids and about 300 flavonoids. In addition to glycoside derivatives, licorice contains several other minor triterpene aglycones (liqueurigenin (LTG), licochalcone A (LCA), licochalcone E (LCE), and glabridin (GLD), which together with GL, are denoted by the term “glycyrrhizin”. Thus, glycyrrhizin is not a chemically pure compound but is a mixture of related substances, the main active component of which is GL [6]. The active ingredients contained in GL have been studied extensively since long time ago. As a result of these studies, the following effects of GL were identified: antihemolymphocoagulating, lymphostimulating, anti-inflammatory, analgesic, antiallergic, hypolipidemic, antioxidant, antitoxic, hepatoprotective, immunotropic, antimicrobial, antitumor, and which is especially important in the present period, antiviral [4,5,8].

Mechanisms of antiviral activity of glycyrrhizic acid

Publications on the antiviral activity of GL appeared over 30 years ago, and publications on GL activity against SARS-associated coronavirus emerged over 20 years ago. It follows from the literature that GL can be active against a wide range of viruses (Figure 1). GL is used to treat chronic viral hepatitis B and C in China and Japan, its derivatives are used against herpes viruses, alpha, and flaviviruses, human immunodeficiency virus, vaccine virus, type I poliovirus, papillomavirus, vesicular stomatitis virus, Epstein-Barr virus, SARS associated coronaviruses causing SARS and influenza A / H1N1 virus [4,9]. However, the antiviral activity of GL was demonstrated only in in-

vivo experiments on developing chicken embryos and mice, while a detailed analysis of the antiviral action of GL and, most importantly, the main mechanism of the development of the antiviral effect has not been addressed. Presenting the antiviral effect of glycyrrhizin on SARS-associated coronavirus happened in 2003. According to the results of the study, it turned out that the effect of glycyrrhizin was stronger than the actions of such reference drugs as ribavirin, 6-azauridine, pyrazofurin, and mycophenolic acid. However, in vitro studies have not proven the early effect of GL in vivo, i.e. GL does not have direct virucidal activity, but acts

indirectly [4,9]. The indirect antiviral effect of GL can be manifested through the cell-virus interaction. This hypothesis is supported by virtual studies on the use of GL in coronavirus infections, as a result of which it was confirmed that GL prevents the adsorption of virus on cellular receptors. It should be clarified that GL activity is manifested only in the early stages of viral reproduction. When the virus binds to receptors, the virus is captured by cells, or the virus is deproteinized in the cytoplasm [9,10]. Moisy *et al.* describe another mechanism of the antiviral effect of GL [11].

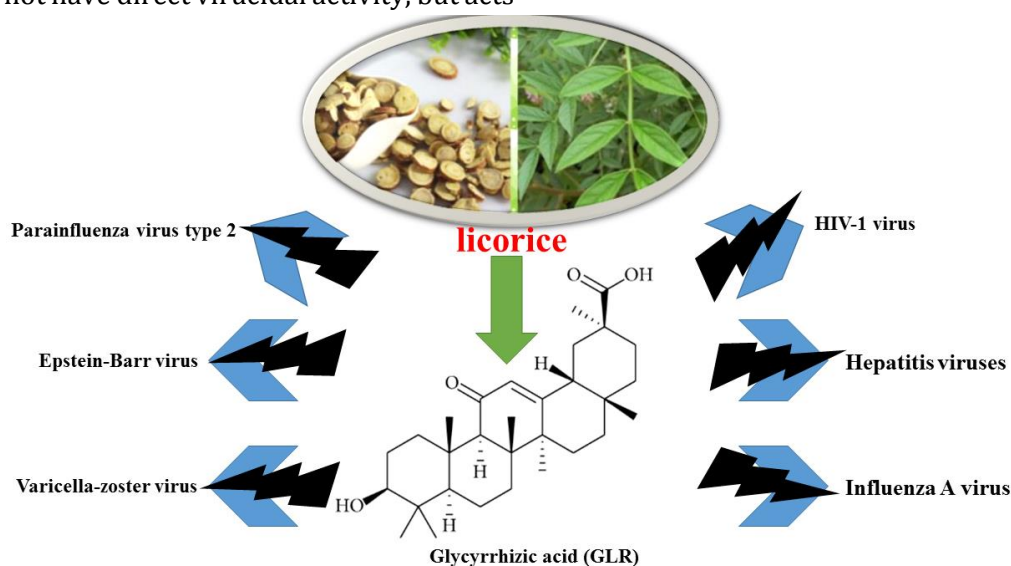


FIGURE 1 Antiviral effects of GLR against some viruses in vitro

In the life cycle of the influenza virus, for example, the so-called HMGB1 protein plays an important role, which binds to the viral nucleoprotein in the nucleus of the infected cell, which initiates the polymerase of the

virus and promotes the growth of the virus. GL interferes with this binding; as a result, the polymerase activity decreases, and the process of viral reproduction slows down [11].

TABLE 1 The mechanism of action of GL and its active components on virus-associated infections

The active component of licorice	Mechanism of action	Viral infection
GL and its monoammonium salt	Increases the number of T4 lymphocytes and decreases the content of viral antigen	HIV
GL and its monoammonium salt	Inhibits virus reproduction	HHV (HHV-6, HHV-7) Human herpes virus
GL	Damages the progen of virions, acts at the stage of viral replication,	HSV HSV-1 Herpes simplex virus

	enhances suppression of viruses	
GL	Slows down virus replication	Hepatitis A, B and C viruses (HAV, HBV, HCV)
GL	Inhibits virus reproduction	H5N1 Bird flu HPV
GL	Inhibits virus reproduction	Human papillomavirus
GL	Inhibits reproduction of the virus; induces the synthesis of nitric oxide synthase; reduces the accumulation of platelets in the lungs; reduces the amount of pro-inflammatory cytokines	SARS-associated coronaviruses

As can be seen from Table 1, the main antiviral effect of GL and its derivatives is due to disturbances in the reproductive cycle of the virus. Since GL has an immunotropic ability, it was long believed that the substance exerts an antiviral effect by potentiating the production of interferon γ in vitro and in vivo and stimulating the secretion of interleukin-2, inducing the production of interferon by peripheral lymphocytes [4]. In their in vivo studies, Utsunomiya *et al.* [12] proved that the decrease in the titer of the virus in animals when using GL occurs due to the initiation of their antiviral activity, i.e. due to the activation of T cells and their production of interferon γ . However, studies by other authors have demonstrated the ability of GL to induce interferon α [4,13,14]. The mechanism of action of GL in SARS-associated coronavirus infection is similar to that of other viral pathologies, but it is more effective in manifestations. Against SARS-associated coronavirus infection, GL acts by inhibiting replication, suppressing the cytopathic effect of the virus, inhibiting its adsorption and penetration into cells. It is believed that the underlying inhibition is related to the ability of GL to induce the synthesis of nitric oxide synthase, which inhibits viral replication. However, the rapid metabolism of GL limits its action, preventing effective concentration. It has long been known that GL may also be useful in the treatment of upper respiratory

tract infections, and hence in acute respiratory distress syndrome without acute bacterial infections. The action of GL in this dangerous pathogenetic manifestation of coronavirus is based on the product's ability to reduce the accumulation of platelets in the lungs and the amount of pro-inflammatory cytokines released by activated inflammatory cells in the initial phase of the syndrome. The presence of a lymphatic stimulating effect in GL, in turn, will contribute to an increase in lymph flow and capillary circulation in the lung tissue, which will create an additional potentially beneficial effect [5,9,10]. Available evidence suggests that SARS-CoV-2 infection is actively involved in the induction of oxidative stress. Moreover, SARS-CoV-2 causes oxidative stress directly, i.e. increases the production of reactive oxygen species (hydrogen peroxide (H_2O_2), superoxide radical anion ($O_2^{\cdot-}$), singlet oxygen (1O_2), hydroxyl radical ($\cdot OH$), and peroxynitrite ($ONOO^-$)), and indirectly, suppresses the host's antioxidant defense. The following specific mechanisms of free radical overproduction in COVID-19 have been suggested. It is known that respiratory viruses, by stimulating enzymes that generate reactive oxygen species (NADPH oxidase, xanthine oxidase, and inducible NO synthase), promote increased production of free radicals. Also, during its development, the COVID-19 virus interacts with the CD147 receptor of erythrocytes, penetrates the cell, destroys

hemoglobin, and releases iron, which is involved in the formation of reactive oxygen forms. Besides, COVID-19 increases the activity of angiotensin II, which can double the production of reactive oxygen forms in vivo by activating NADPH oxidases. The observed granulocytosis in response to infection with SARS-CoV-2 also promotes the production of superoxide ions of the ROS type, which causes additional production of pro-inflammatory cytokines [17]. When considering the antiviral mechanisms of GL, its antioxidant effect should also be noted. As a result of the research of a group of scholars, it has been shown that glycyrrhizin prevents the induction of oxidative stress in influenza A, and as an antioxidant, it inhibits viral replication and the expression of anti-inflammatory genes caused by the virus [17]. The antiviral activity of GL has been confirmed by the work on the functional design of its derivatives. As a result of such studies, esters with d-amino acids, nicotines, 4-methoxycinnamate of 18 α -glycyrrhizic acid, a combination of glycyrrhizic acid with a dipeptide-glutamyl-tryptophan (drug Orvilax), conjugates triterpenic acids with amino sugars and monoglycosides, saponin amides. The above-modified derivatives are considered promising natural compounds with an antiviral effect, based on which anti-coronavirus drugs can be created. [17,18,19,20]. Therefore, considering the antiviral mechanisms of GL in SARS-associated coronavirus infection, its antioxidant effect and the antioxidant effect of licorice products should be noted. Previous research has shown that GL exhibits antioxidant activity in a model of lipid peroxidation in the liver of mice. Glycyrrhizin,

as the main component of licorice roots, interacting in particular with singlet O₂, is a trap for free radicals and interacting with the respiratory chain of liver mitochondria, it generates hydrogen peroxide, which in turn oxidizes critical thiol groups and endogenous pyrimidine nucleotides. Also, glycyrrhizin inhibits the replication of the influenza A (H5N1) virus, and the expression of pro-inflammatory genes induced by it prevents the induction of oxidative stress in influenza infection. At a certain concentration, glycyrrhizin effectively suppresses the formation of reactive oxygen forms in influenza and reduces the H5N1-induced production of cytokines/chemokines [4,18]. Among the products of licorice, which have antioxidant activity against hydroxyl, peroxy, and superoxide radicals, the extract, and powder of licorice root should be noted. Licorice extract protects rat liver microsomes from destruction by lipid peroxidation. Licorice has shown the highest antioxidative effect in human hepatoma cells during H₂O₂-induced oxidative stress and significantly reduced the content of lipid [20]. GL derivatives also have antiviral impact. As a result of the functional design of GL derivatives, esters with d-amino acids, nicotines, 18 α -glycyrrhizic acid 4-methoxycinnamate, a combination of glycyrrhizic acid with a dipeptide - glutamyl-tryptophan (Orvilax preparation), conjugates triterpenic acids, saponins and monoglycosides, as well as heterocyclic amides.

Currently, the range of antiviral drugs containing licorice components includes the following drugs (Table 2).

TABLE 2 Preparations based on active components of licorice with antiviral effect

Drug	Composition	Dosage form	Country - manufacturer
S NMC	0.2% glycyrrhizin, 0.1 cysteine, 2.0% glycine	Solution	Japan
Epigenes	0.1% activated glycyrrhizic acid	Gel, spray, suppositories	Spain

Niglizin	Pentonicotinate Glycyrrhizic Acid	Pills	Russia
Glycyram	Monoammonium salt of glycyrrhizic acid	Tablets, capsules, suppositories	Russia
Phosphogliv	Glycyrrhizic acid and phospholipids	Capsules, tablets,	Russia
Lacrinath	Licorice root powder	Pills	Russia
Viusid	Glycyrrhizic acid, glucosamine, malic acid, trace elements	Powder for internal use	Spain
Carbenoxolone sodium	Disodium salt of acid succinate HA	Tablets, capsules	Great Britain
Gerpigen	Activated glycyrrhizic acid	Cream, spray	Spain
Glyderinin	Glyderinin	Ointment	Kazakhstan

A modern scientific achievement is the use of nanosized, supramolecular aggregates to increase solubility, stability and improve their targeted delivery to the source of the disease [21]. Another ability of GL - a universal non-selective carrier. In particular, it has been shown that, due to its amphiphilic nature, GL is capable of forming self-associates in aqueous and non-aqueous media, as well as water-soluble complexes with lipophilic drugs. Studies carried out by physicochemical methods, i.e. infrared spectroscopy with Fourier transform, scanning electron microscopy, etc., have proven the formation and advantage of the spectrum of action of such Drug Delivery System (DDS). In the experiment, self-associates between GL and molecules of hydrophobic drugs have tens of times greater solubility compared with the parent compound, and *in vivo* studies have demonstrated a significant increase in the bioavailability and therapeutic activity of these supramolecular aggregates, since GL can interact with the cell membrane and change its properties [22].

History of licorice in Azerbaijan

Providing Azerbaijan with plant resources contributed to the accumulation of rich experience in the development of technologies for various dosage forms from herbal medicinal raw materials [23]. Licorice turned out to be the most valuable and promising in terms of research work because the industrial harvesting of licorice root began in Azerbaijan

[24]. Currently, there are 7 types of licorice in Azerbaijan and the quality of the local licorice root is considered one of the best, which allows it to be exported to many countries [24]. The licorice processing in the region is carried out by the Licorice Industrial Park opened in the Agdash region [25]. The plant operating at the park produces environmentally friendly extracts, syrups, and biologically active food supplements from both licorice root and other medicinal plants. Consequently, Azerbaijan has a real industrial platform for the production of herbal antiviral drugs containing active components of licorice root [24,25].

Later, new directions appeared associated with the development of various licorice-containing dosage forms and pharmaceutical products [26]. As part of the subsequent technological development of dosage forms containing glycyrrhizin, multicomponent plant collections were obtained, additionally including calendula, and meadow clover [27]. In further similar studies, the optimal conditions for obtaining herbal complex preparations based on licorice have been studied, and the schemes for the industrial production of immunotropic drugs have been developed with the preparation of appropriate quality standards [28,29]. The technological design of herbal remedies from licorice has been continued by research on obtaining a therapeutic and cosmetic product based on glycyrrhizic acid. By the method of targeted screening, a photocomposition was obtained from licorice root, leaves of

medicinal sage, and Chinese tea (in a ratio of 7: 3: 5), which was included in the cream with a wound-healing effect and antioxidant and antiradical activity [30]. The developed clear tendency of the intensification of inflammatory and viral diseases of the female genital area in the world has contributed to an increase in the incidence of diseases among women in Azerbaijan

Antimicrobial and antifungal efficacy of licorice extract

According to statistical data, the level of inflammatory diseases of the female genital tract in the region is relatively high [31,32]. Consequently, the development of a dosage form containing the components of licorice naked for use in the treatment and prevention of diseases of the female genital tract was a timely and relevant research direction for Azerbaijan [33]. Within the framework of this direction, we have developed vaginal suppositories with a thick extract of licorice nude. In the course of carrying out a scientific study, the developed vaginal suppositories with thick licorice extract have been analyzed for antimicrobial and antifungal activity [34].

Antimicrobial and antifungal impact has been assessed by a disk diffusion test on agar using test cultures of microorganisms ATCC (American Type Culture Collection). [GPH.Ar.1.2.4.0002.15. "Microbiological purity"]. The control substance was a thick extract of licorice nude. According to the result

of our study, microbial growth (positive) was observed in all Petri dishes (Table 3), which demonstrated the absence of direct antimicrobial properties in the developed products.

However, the literature confirms the presence of a decoction of licorice root bare bactericidal effect against a standard culture of *Staphylococcus aureus*, bacteriostatic effect against *E. coli*, and bacteriostatic activity against *Pseudomonas aeruginosa* [34].

The use of a lipophilic base (a mixture of cocoa butter, sea buckthorn, and milk thistle in a ratio of 8: 3: 7) in the technology of the analyzed vaginal suppositories does not allow a thick licorice extract to show direct antibacterial properties. From the literature it follows that the extract rather provides an antimicrobial preservative effect [28,34]. Vaginal suppositories can also be prescribed to prolong the therapeutic effect in the lesion; therefore, this dosage form should not violate the biocenosis of the genitals, as a result of this, further, we analyzed the activity of the studied products against *L. crispatus*, *L. gasseri*, using the disc diffusion method. *L. iners*, *L. jensenii*, *L. Johnsonii*. A thick extract of licorice root was also used as an object of comparison. As a result of studying the antimicrobial action of the proposed vaginal suppositories for lactobacilli species, we observed inhibition of microbial growth in all Petri dishes. A thick extract of licorice exhibited a similar effect (Table 4).

TABLE 4 The results of the analysis of suppository products and thick extract of licorice naked for the manifestation of antimicrobial effect against lactobacilli

Test strains	Presence of zones of inhibition of test strains	
	Vaginal suppositories	Thick extract of licorice
<i>L. crispatus</i>	+	+
<i>L. gasseri</i>	+	+
<i>L. iners</i>	+	+
<i>L. jensenii</i>	+	+
<i>L. Johnsonii</i>	+	+

Conclusion

As can be seen from the above material, an anti-COVID agent should be created based on thorough studies of the nature of the virus itself, the mechanism of its effect on the body, advances in the treatment of this viral infection and using high technologies for the production of medicines. Of course, this antiviral agent must meet the requirements for drugs: its safety, effectiveness, and selectivity, not having pronounced side effects, i.e. harmonizing with the oldest principle of medical ethics "Do no harm" (primum non nocere "Hippocratic Corpus", 430-330). Thus, the development of an antiviral agent based on the components of licorice, exhibiting various pharmacological effects and possessing antioxidant activity, is a promising direction for correcting anti-coronavirus therapy.

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