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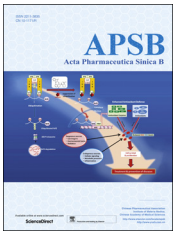

REVIEW

The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb

Liqiang Wang, Rui Yang, Bochuan Yuan, Ying Liu*, Chunsheng Liu**

School of Chinese Pharmacy, Beijing University of Chinese Medicine, Beijing 100102, China

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KEY WORDS

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Glycyrrhizin;
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Chalcone

Abstract Licorice is a common herb which has been used in traditional Chinese medicine for centuries. More than 20 triterpenoids and nearly 300 flavonoids have been isolated from licorice. Recent studies have shown that these metabolites possess many pharmacological activities, such as antiviral, antimicrobial, anti-inflammatory, antitumor and other activities. This paper provides a summary of the antiviral and antimicrobial activities of licorice. The active components and the possible mechanisms for these activities are summarized in detail. This review will be helpful for the further studies of licorice for its potential therapeutic effects as an antiviral or an antimicrobial agent.

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Abbreviations: CCEC, cerebral capillary vessel endothelial; CCL5, chemokine (C-C motif) ligand 5; CVA16, coxsackievirus A16; CVB3, coxsackievirus B3; CXCL10, chemokine, (C-X-C motif) ligand 10; DGC, dehydroglyasperin C; DHV, duck hepatitis virus; EV71, enterovirus 71; GA, 18β-glycyrrhetinic acid; GATS, glycyrrhizic acid trisodium salt; GL, glycyrrhizin; GLD, glabridin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HMGB1, high-mobility-group box1; HRSV, human respiratory syncytial virus; HSV, herpes simplex virus; HSV1, herpes simplex virus type 1; IFN, interferon; IL-6, interleukin-6; LCA, licochalcone A; LCE, licochalcone E; ISL, isoliquiritigenin; LTG, liquiritigenin; MgIG, magnesium isoglycyrrhizinate; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PMN, polymorph nuclear; PrV, pseudorabies virus; TCM, traditional Chinese medicine

*Corresponding author. Tel.: +86 10 84738646; fax: +86 10 84738611.
**Corresponding author. Tel.: +86 10 84738624.
E-mail addresses: liuyliwd@sina.com (Ying Liu), maxliucs@263.net (Chunsheng Liu).

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1. Introduction

Licorice is a very well known herb in traditional Chinese medicine (TCM). In China, it is called "gancao" (meaning "sweet grass") and has been recorded in the *Shennong's Classic of Materia Medica* around 2100 BC. In this book, licorice was supposed to have life-enhancing properties. During the following thousands of years licorice has been present in most of Chinese traditional prescriptions. It was believed to have the functions of nourishing *qi*, alleviating pain, tonifying spleen and stomach, eliminating phlegm, and relieving coughing[1].

Glycyrrhiza uralensis Fisch., *Glycyrrhiza inflate* Bat. and *Glycyrrhiza glabra* L. were prescribed as licorice in *Chinese pharmacopoeia*[2]. They are widespread in Inner Mongolia, Gansu, Heilongjiang, Ningxia, Qinghai and many other provinces in China[3]. The roots and rhizomes are the main medicinal parts of licorice. Numerous studies have revealed many pharmacological activities of licorice, such as antiviral[4,5], anti-inflammatory[6,7], antitumor[8,9], antimicrobial[10,11] and many other activities[12,13]. Among the pharmacological activities of licorice mentioned above, the antiviral and antimicrobial activities have been most commonly reported. Viral and other microbial infections play a critical role in many highly prevalent diseases, especially in developing countries. The development of safe and effective antiviral or antimicrobial agents is very important, and licorice deserves more attention for its outstanding activities.

Licorice contains more than 20 triterpenoids and nearly 300 flavonoids. Among them, glycyrrhizin (GL), 18β-glycyrrhetinic acid (GA), liquiritigenin (LTG), licochalcone A (LCA), licochalcone E (LCE) and glabridin (GLD) are the main active components which possess antiviral and antimicrobial activities. Their chemical structures are listed in Fig. 1.

2. The antiviral active components and their possible mechanisms

Among the components isolated from licorice, 73 bioactive components and 91 potential targets have been identified to date[14,15]. Many studies have demonstrated that two triterpenoids, GL[16,17] and GA[18], are responsible for the antiviral activity. The possible mechanisms for virus prevention of GL and GA, and the viral types are listed in Table 1.

2.1. GL

GL is one of the major compounds isolated from the roots of licorice. In recent years, many studies have confirmed the antiviral activity of GL. Matsumoto et al.[16] reported that GL targeted the release step in which infectious anti-hepatitis C virus (HCV) particles were infecting cells. These findings indicated possible novel roles for GL to treat patients suffering from chronic hepatitis C. In another study, researchers also found that GL treatment inhibited HCV titer and caused 50% reduction of HCV at the concentration of 14 ± 2 μg/mL by inhibiting HCV full length viral particles and their core gene expression[19].

Previous studies showed that intercellular adhesion molecules played an important role in some viral infections, such as human immunodeficiency virus (HIV)[20]. Huang et al.[5] found that the adhesion force and stress between cerebral capillary vessel endothelial (CCEC) cells and polymorph nuclear (PMN) leukocytes were clearly increased in HSV infection; GL perfusion significantly reduced adhesion force and stress between CCEC and PMN.

Zhang's study[21] reported that GL showed a significant improvement of coxsackievirus B3 (CVB3)–induced myocarditis by improving weight loss profile, reducing serological levels of cardiac enzymes and increasing survival rate. This effect was evidenced by significantly reduced expression of proinflammatory cytokines, such as nuclear factor–κB, interleukin-1β and interleukin-6. The inhibition of CVB3-induced nuclear factor–κB activity blocks the degradation of nuclear factor–κB inhibitor IκB. All these data suggested that GL had an effect on CVB3-induced myocarditis and may present as a new therapeutic approach for the treatment of viral myocarditis.

Soufy et al.[22] found that GL had excellent immunostimulant properties and induced a synergistic effect to duck hepatitis virus (DHV) vaccine by activating T lymphocyte proliferation. Four groups, control, GL treated, vaccinated with live attenuated DHV vaccine and GL treated and vaccinated, were investigated. Among them, treatment with GL alone or with DHV vaccine showed good immune stimulant and antiviral effects against DHV. GL combined with DHV vaccine produced higher antibody titers against DHV than by the use of DHV vaccine alone.

Several studies have demonstrated that GL showed a significant inhibiting effect to influenza virus. At a concentration of 100 μg/mL (a therapeutically achievable concentration), GL weakened

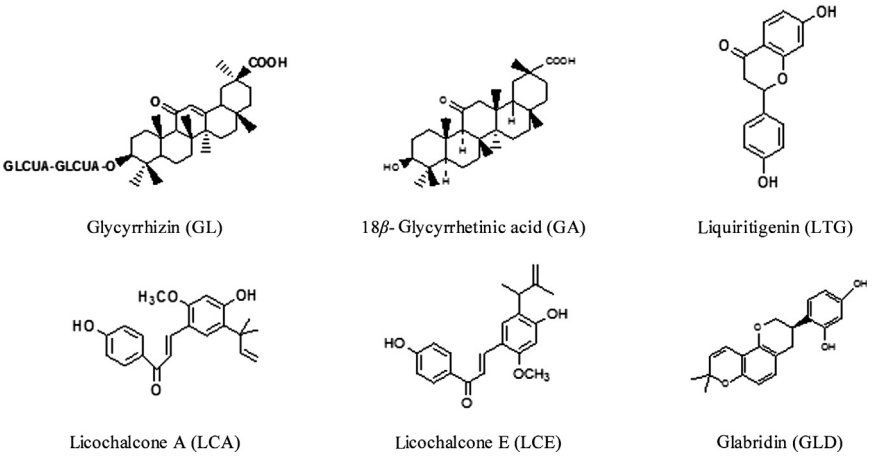

Figure 1 The chemical structures of the antiviral activity or antimicrobial components in licorice.

Table 1 The antiviral active components and their possible mechanisms for virus prevention.

Component	Antiviral mechanism	Viral type
GL	Affect release step while infectious HCV particles are infecting cells.	HCV
	Inhibit HCV full length viral particles and HCV core gene expression.	
	Reduce adhesion force and stress between CCEC and PMN.	HSV
	Block the degradation of nuclear factor κB inhibitor IκB.	CVB3
	Activate T lymphocyte proliferation.	DHV
	Weaken H5N1-induced production of CXCL10, IL-6 and CCL5, and suppress H5N1-induced apoptosis.	H5N1
	Reduce HMGB1 binding to DNA, and inhibit influenza virus polymerase activity.	Influenza virus
	Inactivate CVA16 directly, while the effect of anti-EV71 is associated with an event(s) during the virus cell entry.	CVA16 EV71
	Establish a resistance state to HSV1 replication.	HSV1
GA	Reduce the levels of viral proteins VP2, VP6 and NSP2 at a step or steps subsequent to virus entry.	Rotavirus
	Prevent viral attachment, internalization and stimulate IFN secretion.	HRSV

H5N1-induced production of chemokine (C-X-C motif) ligand 10 (CXCL10), interleukin 6 (IL-6) and chemokine (C-C motif) ligand 5 (CCL5), and suppressed H5N1-induced apoptosis[23]. The high-mobility-group box1 (HMGB1) DNA-binding site was indicated to enhance influenza virus replication. GL could reduce HMGB1 binding to DNA, which inhibited influenza virus polymerase activity[24]. Smirnov's study[25] indicated that GL could be considered a promising agent for the treatment of influenza.

Wang's study[17] revealed that GL was an antiviral component in licorice against enterovirus 71 (EV71) and coxsackievirus A16 (CVA16) infection with defined mechanisms. It activated CVA16 directly, while the effect of anti-EV71 was associated with an event during the cell entry for virus.

GL was also a strong inducer of the autophagy activator Beclin 1. After 24 h of treatment, Beclin 1 production induced by GL was more than two fold higher than that was induced by rapamycin, the reference compound. GL was a strong inducer of Beclin 1, which inhibited the replication of herpes simplex virus type 1 (HSV1)[26]. Therefore, GL possessed its anti-HSV1 activity by establishing a resistant state to HSV1 replication.

Above all, GL is an effective antiviral compound against HCV, HIV, CVB3, DHV, EV71, CVA16, HSV and H5N1 by weakening virus activity, such as inhibiting virus gene expression and replication, reducing adhesion force and stress, and reducing HMGB1 binding to DNA. The compound also enhances host cell activity, *e.g.*, by blocking the degradation of IκB, activating T lymphocyte proliferation and/or suppressing host cell apoptosis.

2.2. GA

Compared with GL, studies of the antiviral activity of GA are limited. GA treatment inhibited rotavirus replication, which likely occurred at steps subsequent to virus entry. GA reduced rotavirus yields by 99% when it was added to infected cultures post-viral adsorption. The levels of viral proteins VP2, VP6 and NSP2 were substantially reduced[27]. GA also showed potent anti-human respiratory syncytial virus (HRSV) activity. It inhibited HRSV mainly by internalization, stimulating interferon (IFN) secretion, and preventing viral attachment[18].

There is a difference between the antiviral profiles of GA and GL. GA has activity against rotavirus and HRSV. However, the antiviral mechanisms of these compounds are similar. GA exerts its antiviral activity also by inhibiting virus replication, preventing viral attachment or enhancing host cell activity.

3. The antimicrobial active components and their possible mechanisms

Increasing antibiotic resistance has resulted in an urgent need for alternative therapies to treat diseases. In recent years, many studies have shown that licorice aqueous extract[28], ethanol extract[29] and supercritical fluid extract[30] have potent effects in inhibiting the activities of Gram-positive bacteria and Gram-negative bacteria, such as *Staphylococcus aureus*[31], *Escherichia coli*[32], *Pseudomonas aeruginosa*[33], *Candida albicans* and *Bacillus subtilis*[34]. These extracts are also being considered as potential alternatives to synthetic fungicides, or as lead compounds for new classes of synthetic fungicides. Based on the above inhibitory activities against bacteria, licorice may serve as an alternative therapy for treating dental caries, periodontal disease, digestive anabrosis and tuberculosis. The possible mechanisms for antimicrobial effects of the active components and the microorganism types were listed in Table 2.

3.1. GA

Methicillin-resistant *S. aureus* (MRSA) has become a main source of infection in both hospitals and the community. Increasing antibiotic resistance in *S. aureus* strains has created a need for other therapies to treat disease. GA showed bactericidal activity to destroy MRSA by decreasing the expression of *SaeR* and *Hla*, the key virulence genes of MRSA[31]. Studies also indicated that GA produced a better Th1 immune response than Th2 response. This Th1-immunological adjuvant activity would be helpful in the treatment of Th1-related disease caused by *C. albican*[35].

3.2. Chalcones

Zhou et al.[36] suggested that licochalcone E (LCE) could be used for chemical synthesis of novel anti–*S. aureus* compounds which could reduce the production of α-toxin in both methicillin-sensitive *S. aureus* (MSSA) and MRSA. Licochalcone A (LCA) and glabridin (GLD) showed antifungal activity on *C. albicans*. They were both potent antifungal agents against *C. albicans*. LCA (0.2 μg/mL) inhibited biofilm formation by 35%–60% and both LCA and GLD had strong inhibitory effects (>80%) in preventing yeast-hyphal transition in *C. albicans*[37].

Table 2 The antimicrobial active components and their possible mechanisms for microbe prevention.

Component	Antimicrobial mechanism	Microbial type
GA	Decrease the expression of *SaeR* and *Hla*, which are the key virulence genes of MRSA.	*S. aureus*
	Exert the Th1-immunological adjuvant activity.	*C. albicans*
LCA	Inhibit the biofilm formation and prevent yeast-hyphal transition.	*C. albicans*
LCE	Reduce the production of α-toxin.	*S. aureus*
GLD	Prevent yeast-hyphal transition.	*C. albicans*
LTG	Decrease the production of α-hemolysin.	*S. aureus*

3.3. *Liquiritigenin*

α-Hemolysin is an important exotoxin in the pathogenesis of *S. aureus* infections. Such infections are associated with a broad spectrum of diseases ranging from endocarditis to minor skin infections, toxinoses, and lethal pneumonia. Liquiritigenin (LTG), one of the most significant active components in licorice, can prevent human lung cells (A549) from α-hemolysin-mediated injury by decreasing α-hemolysin production[38]. Such data suggest that LTG is potentially useful in developing drugs which target staphylococcal α-hemolysin.

In summary, one triterpene (GA) and four flavones (LCA, LCE, GLD and LTG) seem to account for much of the antimicrobial activity in licorice. These compounds can decrease the expression of microbe genes, inhibit microbe growth and reduce the production of microbe toxin.

4. Discussion

Presently we have summarized the antiviral and antimicrobial activities of licorice. Many studies found that several components were responsible for the antiviral and antimicrobial activities through different mechanisms. Licorice contains more than 20 triterpenoids and nearly 300 flavonoids. Among them, only two triterpenes, GL and GA have been reported to have antiviral effects. They can weaken virus activities by inhibiting virus gene expression and replication, reducing adhesion force and stress, and reducing HMGB1 binding to DNA. They can also enhance host cell activities by blocking the degradation of IκB, activating T lymphocyte proliferation and suppressing host cell apoptosis. In contrast, flavonoids, especially chalcones, play an important role in the treatment of bacterial infection by decreasing expression of bacterial genes, inhibiting bacterial growth and reducing the production of bacterial toxin.

In addition, many studies have reported that the six active compounds listed in this paper, GL, GA, LCA, LCE, GLD and LTG, possess other activities. For example, GL and GA also have antitumor[39,40], anti-inflammatory[41,42], and immunoregulatory activities[12,43,44]. LCA, LCE, LTG and GLD also have inhibitory effects on diabetes[45–48]. All of these reports demonstrate potentially broad applications for these agents. In addition, there are many other compounds isolated from licorice with different pharmacological activities. For example, isoliquiritigenin (ISL) shows effective immunoregulatory activity[49], glabrol has an inhibitory effect on diabetes[50], and dehydroglyasperin C (DGC) has hepatoprotective activity[51].

Among the six compounds listed in this paper, only GL has been clinically developed as a drug. As the most important marker component in licorice, the development of GL preparations has a long history in China, from GL tablets to ammonium glycyrrhizinate, diammonium glycyrrhizinate and magnesium isoglycyrrhizinate (MgIG). All of the above GL preparations possess antiviral and antimicrobial activities. Diammonium glycyrrhizinate inhibits cell infection by pseudorabies virus (PrV) and decreases cell apoptosis during PrV infection[52]. Compared with diammonium glycyrrhizinate, the fourth generation GL preparation, MgIG, has better lipophilic properties, higher targeting activity and fewer adverse reactions. It has been used in treating liver disease[53–55], pulmonary fibrosis[56] and testicular injuries[57]. However, reports about mechanisms of antiviral and antimicrobial activities of MgIG are still very limited. The development of new licorice preparations will improve the safety and efficacy of licorice-related products.

In many African countries with poorly developed health care systems, viruses and bacteria are significant sources of disease. More than 2 billion people have been exposed to HBV over the world, and the situation in some areas of Africa is much more serious[58]. The development of effective and affordable licorice-related medicines could introduce dramatic improvements in treating the many prevalent diseases of third world populations. It is hoped that the present work will facilitate the development of improved licorice preparations with antiviral and antimicrobial activities.

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