



Review Article

Scope of *Glycyrrhiza glabra* (Yashtimadhu) as an Antiviral agent: A Review

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The persistence of drug resistant viruses has become a major problem. Antiviral therapy has targeted various aspects of viral replication steps. Nowadays pharmaceutical industries are focusing to develop new antiviral agents for the treatment of the multidrug resistant viral infections. There is a large amount of data published stating the efficacy of various medicinal plants useful against many viruses. Yashtimadhu (*Glycyrrhiza glabra*) is one such plant which has shown remarkable activity against large number of viruses. In ancient Ayurvedic System, more than 1250 preparations are described containing Yashtimadhu as one of its constituents. *Glycyrrhiza glabra* or Licorice has been proven beneficial against many DNA viruses such as Varicella zoster virus, Kaposi sarcoma-associated herpesvirus, Herpes Simplex Virus-1, Epstein-Barr virus, Human Cytomegalo virus, etc and RNA viruses such as Influenza A virus (IAV), H5N1 virus, H1N1 virus, Hepatitis C virus, Newcastle disease virus, Rotavirus, SARS-associated coronavirus, Human Immunodeficiency Virus etc. This review has tried to give an account of antiviral activity of various bioactive molecules of Yashtimadhu (*Glycyrrhiza glabra*) against various viruses.

Introduction

Viral diseases are spreading with alarming speed across the continents and countries due to the progress in global travel. Viral diseases are difficult to control due to their metabolic properties and fast emergence drug resistance.

A major problem in the fight against viruses is their rapid adaptation and development of drug-resistance as well as the emergence of new hybrid viruses. Common medications are often inadequate and show a variety of side effects. In the past few years, natural

remedies came more and more in the center of interest. (Cecilia Perera et al, 2012) Antiviral treatment is necessary to limit the severity and duration of the disease in both immunocompetent and immunocompromised individuals. Emerging resistance to antiviral drugs highlights the importance of testing the susceptibilities of isolates to current therapy. Also, screening the antiviral activity of new antiviral agents is important to establish efficient treatment in cases of resistance to the antiviral drugs and for safer treatment, as in pregnant patients. (Shebl RI, et al, 2012)

The World Health Organization (WHO) estimated that about an 80% population of developing countries relies on traditional medicines, mostly plant drugs, for their primary health care needs. Particularly in rural India, uses of raw plant products as well as some concoction of Ayurvedic medicines are sought after to a great proportion, because of cheap availability, and in urban areas too those are popular (Korhalkar Anagha et al, 2014)

There is currently a large and ever-expanding global population base that prefers the use of natural products in treating and preventing medical problems. This has influenced many pharmaceutical companies to produce new antimicrobial formulations extracted from plants or herbs. (S.A.A. Jassim et al, 2003)

The antiviral drugs are expensive and are far beyond the means of most developing countries. The development of safe, effective and inexpensive antiviral drugs is among the top global priorities of drug development, as many viruses are not yet curable and mortality rates are high. Therefore, it is essential to continue the search for useful and novel natural antiviral agents, which can be expected to prolong the efficacy of drug therapy. Viruses are

constantly evolving and have been developing new ways to evade the immune system. All of these render the quest of antiviral therapy challenging since it is difficult to identify unique biochemical features of viruses that may be suitable for selective attack. (Mishra et al., 2013)

This article describes potential antiviral properties of *Glycyrrhiza glabra* against a diverse group of viruses, and suggests screening its potential as broad-spectrum antiviral agent against emerging viral infections.

Materials and Methods

Various scientific research and review articles published in English from 2000 to 2014 were identified through pub med and Google scholar websites using MeSH terms, *Glycyrrhiza glabra*, Antiviral agents, Glycyrrhizic acid, Licorice, Virus Replication/drug effects.

More than 160 research articles including few review papers were searched. These articles were grouped according to antiviral activities against DNA or RNA viruses in this review.

DNA Viruses

Varicella zoster virus

Licorice is one of the most widely used herbal drugs around the world, being present in most pharmacopoeias of eastern and western countries. Rania I. Shebl et al studied the cytotoxicity of liquorice powder extract and acyclovir on Vero cells by using crystal violet uptake assays. This study has found that Glycyrrhizin in the crude form had a low antiviral activity against VZV compared with acyclovir and interferon. (Rania I. Shebl et al, 2012)

Kaposi sarcoma- associated herpesvirus-

Francesca Curreli et al showed for the first time that, Glycyrrhizic acid (GA) selectively promoted cell death in latent KSHV (Kaposi sarcoma-associated herpes virus) –infected cells and that, at the active concentration, it was not toxic for uninfected cells. GA altered latent gene transcript levels and that latent infection with KSHV in B lymphocytes could be terminated by Glycyrrhizic acid. This study has demonstrated that GA disrupted latent KSHV infection by downregulating the expression of latency-associated nuclear antigen (LANA) and upregulating the expression of viral cyclin and it selectively induced cell death of KSHV-infected cells. In addition, Curreli found that the cells treated with GA showed higher levels of phosphorylated (active) p53, which resulted in cell cycle arrest at the G1 checkpoint and upregulated expression of the KSHV cyclin protein (v-cyclin). (Francesca Curreli, et al, 2005)

Herpes Simplex Virus-1

A) Huang W, Chen X, et al studied a potential role of glycyrrhizin in disrupting cellular adhesion in HSV. They isolated rat cerebral capillary vessel endothelial cells (CCECs) and polymorphonuclear leukocytes (PMN) and evaluated intercellular adhesion between these cells by micropipette aspiration technique. In this study they found that Glycyrrhizin perfusion significantly reduced adhesion force and stress between CCEC and PMN. Thus they concluded that, glycyrrhizin attenuated inflammatory responses in HSV by inhibition of adhesion between CCEC and PMN. (Huang W et al, 2012)

B) Masoud Sabouri Ghannad, et al in Iran investigated the effects of *Glycyrrhiza*

glabra (liquorice root) on HSV-1. This study assessed the efficacy and the effect of the elapsed incubation time of treating the Vero cells infected with HSV-1 by *Glycyrrhiza glabra* and also the effect of cells pretreatment with licorice root extract, preincubation of virus with licorice root extract, and the antiviral activity was assessed.

They incubated the Vero cells after adding different concentrations of aqueous extracts of *Glycyrrhiza glabra* for various time courses. Cytotoxicity assay done in this study showed that there was significant difference in the efficacy of the extract with regard to incubation period between one and four hours, one and eight hours, four and 12 hours, and eight and 12 hours. This study also showed that there was a significant difference with regard to efficacy among the pretreatment of cells with extract for two hours, incubation of virus with extract for one hour, incubation of virus with extract for two hours. The results of the study speculated that the suppression of HSV-1 replication in Vero cells occurred by interruption of the late stages of genes expression. This study concluded that *Glycyrrhiza glabra* could be used as a novel antiviral medication. (Masoud Sabouri Ghannad et al, 2014)

C) Sekizawa T, et al , from Sendai, Japan, studied the effect of glycyrrhizin (GR), on herpetic encephalitis that was inflicted on mice by inoculation of herpes simplex virus 1 (HSV-1). They inoculated glycyrrhizin intraperitoneally in mice suffering from herpetic encephalitis. This study has found that it increased their survival rate in average about 2.5 times. They also found that glycyrrhizin reduced HSV-1 replication in the brain to 45.6%. These results demonstrated that glycyrrhizin had stimulative effect on the mouse defense

system against HSV-1 infection. (Sekizawa T, et al, 2001)

4) Epstein–Barr virus

A) Jung Chung Lin has reported in this paper that Glycyrrhizic acid (GL) was found to be active against EBV replication in superinfected Raji cells in a dose-dependent fashion. The time of addition experiments suggested that GL interfered with an early step of EBV replication cycle (possibly penetration), They also found that GL had no effect on viral adsorption and it did not inactivate EBV particles. He suggested that GL represented a new class of anti-EBV compounds with a mode of action different from that of the nucleoside analogs that inhibit viral DNA polymerase. (Jung Chung Lin, 2003)

B) Lin JC, et al, investigated the effects of 15 Glycyrrhizic acid (GL) derivatives against EBV infection by scoring the numbers of cell expressing viral antigens and quantifying EBV DNA copy numbers in superinfected Raji cells. They identified seven compounds out of the 15, which were active against EBV and all showed dose-dependent inhibition as determined by both assays.

The findings of this study were that, 1) the introduction of amino acid residues into the GL carbohydrate part enhanced the antiviral activity in three of the seven active compounds, 2) the introduction of potassium or ammonium salt to GL reduced the antiviral activity, 3) the substitution of Glu(OH)-OMe by Glu(OMe)-OMe, completely abolished its antiviral activity and 4) the metabolic product of GL, 18beta-glycyrrhetic acid (18beta-GA or GA), was 7.5-fold more active against EBV than its parental compound GL. (Lin JC, et al, 2008)

5) Human cytomegalovirus

W Xing, et al, investigated the therapeutic efficacy of traditional Chinese medicine Reduqing (RDQ) against human cytomegalovirus (HCMV) in clinical and its antiviral activity in vitro. (Reduqing (RDQ)-A Chinese herbal formula containing Paris polyphylla, Dandelion, Woad, and Licorice). They detected HCMV antibody to detect active HCMV infection in fourteen patients and treated with Reduqing (RDQ). They administered the drug orally, three times a day, for 18-30 days. And they evaluated the efficacy by ELISA, PCR and other methods. The in vitro inhibitory activity of RDQ against HCMV AD169 was carried out on human embryo lung fibroblasts (HEL) by cytopathic effect inhibition method. This study found that, after 18-30 days of treatment, all showed HCMV-IgM negative conversion, HCMV DNA negative conversion in 7/10 cases, and virus excretion by urine and cervix secretion was inhibited in 4/4 and 1/1 case. The in vitro study showed that the maximal tolerance dosage (TD0) of RDQ was 20 micrograms/L, the minimal therapeutic concentration (MTC) was 5 micrograms/L. The results of the study indicated that, RDQ had anti-HCMV activity in vitro and the effect increased with its concentration. These results suggested that, RDQ was a safe, valuable drug for inhibiting HCMV infection especially during pregnancy. (W Xing, et al, 2000)

RNA Viruses

6) Influenza A virus (IAV)

Wolkerstorfer A, et al investigated the mechanism by which glycyrrhizin (GL), protected cells from infection with influenza A virus (IAV). They found that GL treatment led to a clear reduction in the number of IAV-infected human lung cells as

well as a reduction in the CCID50 titer by 90%. This study found that, the antiviral effect was limited to one or two virus replication cycles, the antiviral effect of GL was abolished by treatment 1h after virus infection. They found that pre-treatment and treatment during and after virus adsorption led to a reduction in the cytopathic effect reduced viral RNA within the cells and in the cell supernatants, and reduced viral hemagglutination titers. They found that the virus uptake was reduced in various GL-treated cells. This study concluded that the antiviral activity of GL was mediated by an interaction with the cell membrane which most likely resulted in reduced endocytotic activity and hence reduced virus uptake.(Wolkerstorfer A, et al 2009)

7) H5N1 virus

A) Martin Michaelis, et al investigated the effect of approved parenteral glycyrrhizin preparation-(Stronger Neo-Minophagen C-SNMC) on H5N1 virus replication. They found that, Glycyrrhizin 100 lg/ml impaired H5N1-induced production of CXCL10, interleukin 6, and CCL5 and inhibited H5N1-induced apoptosis but did not interfere with H5N1 replication. This study concluded that, the therapeutic concentrations of a clinically approved parenteral preparation of glycyrrhizin interfered with highly pathogenic H5N1 influenza A virus-induced pro-inflammatory gene expression in human MDMs without affecting NK cell activity.
(Martin Michaelis, et al,2010)

B) Michaelis M, , et al, in their further work with effect of Stronger Neo-Minophagen-SNMC on highly pathogenic influenza A H5N1 virus replication, studied H5N1-induced pro-inflammatory responses in lung epithelial (A549) cells. They observed that,

therapeutic glycyrrhizin concentrations substantially inhibited H5N1-induced expression of the pro-inflammatory molecules CXCL10, interleukin 6, CCL2, and CCL5 and also diminished monocyte migration towards supernatants of H5N1-infected A549 cells. So the study group concluded that glycyrrhizin could be included in the arsenal of potential drugs for the treatment of H5N1 disease.(Michaelis M, et al 2011)

8) H1N1

U Grienke, et al found on a shape-focused virtual screening approach, that, the roots of *Glycyrrhiza glabra* L. (licorice) had an accumulation of molecules that showed 3D similarities to influenza NA (neuraminidase) inhibitors. They found twelve such constituents, out of which, biochanin B, and glabrone showed distinct inhibition of the cytopathic effect in MDCK cells. They performed chemiluminescence (CL)-based NA inhibition assays on the target level using the NA of different influenza virus strains including A/342/09 (H1N1), an oseltamivir-resistant virus isolate. This study found that, 11 compounds out of twelve, showed IC50s in the low micromolar to even nanomolar range. (Grienke U, et al, 2013)

9) Hepatitis C virus

A) This study included patients with chronic hepatitis C, nonresponders, (genotype 1/cirrhosis) to interferon therapy. The study evaluated the short-term (4-wk) feasibility and efficacy on serum ALT of three or six times per week i.v. glycyrrhizin therapy in European patients. This study found that the percentage ALT decrease at the end of treatment was 26% and 47% for the three times per week and six times per week treatment group, respectively and at the end

of active treatment, 10% (four of 41) and 20% (three of 15) of the patients reached normal ALT levels for the same two groups. The ALT lowering effect disappeared after cessation of treatment. No major side effects were observed. Van Rossum TG et al suggested that, Glycyrrhizin treatment induced a significant ALT decrease in patients with chronic hepatitis C and six times per week treatment was more effective than three times per week.(van Rossum TG et al,2001)

B) Usman A Ashfaq et al evaluated the antiviral effect of Glycyrrhizin (GL) against Hepatitis C Virus. HCV infected liver cells were treated with GL at non toxic doses and Hepatitis C Virus titer was measured by Quantitative real time RT-PCR. The results demonstrated that Glycyrrhizin inhibited HCV titer in a dose dependent manner. They also showed that Glycyrrhizin exhibited synergistic effect when combined with interferon and that GL inhibited Hepatitis C full length viral particles and HCV core gene expression or functions in a dose dependent manner.(Usman A Ashfaq, et al 2011)

10) Newcastle disease virus

Muhammad Ovais Omer et al evaluated the comparative anti-viral efficacy and toxicity of *Glycyrrhiza glabra* aqueous extract and ribavirin against the Newcastle disease virus. The embryonated eggs were inoculated with the virus and the virus was identified by hemagglutination inhibition test. They used three different concentrations i-e., 30 mg/100 ml, 60 mg/100 ml, and 120 mg/100 ml of the *Glycyrrhiza* aqueous extract and 10 µg/ml, 20 µg/ml, and 40 µg/ml ribavirin in deionized water and evaluated their toxicity and anti-viral activity in the embryonated eggs. The researchers found that 60 mg/100

ml concentration of *Glycyrrhiza* extract produced no toxicity in the embryonated eggs and showed anti-viral activity against the virus.(Muhammad Ovais Omer,et al,2014)

11) Rotavirus

In this study Karen Knipping, et al, investigated 150 edible plant extracts and some of their natural compounds for in vitro anti-rotavirus infection effects. The viruses were grown in MA104 cells and concentrated by ultracentrifugation. All plant extracts were tested as a first screening in an antiviral titration assay with MA104 cells in the concentrations of 400 and 500 µg/ml in medium. This study found only four compounds that showed an inhibitory effect. The study revealed that 18β-glycyrrhetic acid from *Glycyrrhiza glabra* had the strongest antiviral activity (IC₅₀ 46 µM). (Karen Knipping, et al,2012)

12) SARS-associated coronavirus

J Cinatl, et al, assessed the antiviral activities of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients with SARS admitted to the clinical centre of Frankfurt University, Germany. They studied the cytopathogenicity induced by the virus 72–96 hours after infection in 96-well microplates on confluent layers of Vero cells. They found that, in addition to inhibition of virus replication, glycyrrhizin inhibited adsorption and penetration of the virus. They had also observed that, Glycyrrhizin was less effective when added during the adsorption period than when added after virus adsorption. It was demonstrated by them that, the expression of viral antigens was much lower in cultures treated with 1000 mg/L of glycyrrhizin than

in any other culture; and high concentrations of glycyrrhizin(4000 mg/L) completely blocked replication of the virus. The results of the study showed that glycyrrhizin induced nitrous oxide synthase in Vero cells and that virus replication was inhibited when the nitrous oxide donor was added to the culture medium.(J Cinatl et al.,2003)

13) Human Immunodeficiency Virus

A) Yao WH, et al evaluated the effect of glycyrrhizin on peripheral T-lymphocyte subset in AIDS patients. Forty AIDS patients were randomly divided into a treatment group (treated with HAART+ Compound Glycyrrhizin) and a control group (treated with HAART), for 6 months. This study found that after 6 months of treatment, the expressions of CD8+ and CD38+ of PBL in the treatment group were found to be lower than that in the control and CD4+ T count rose more significantly. They concluded that Compound Glycyrrhizin could lower the expression of active T-lymphocyte subset, inhibited HIV and helped immune reconstitution.(Yao WH, et al,2006)

B) Julia Hupfeld et al had mentioned in their review that, in vitro, Glycyrrhizin had an IC50 of 0.15 mM, and that its action seemed to be mediated through inhibition of virus binding to the host cell and inhibition of protein kinase C (PKC). Additionally it was mentioned in this review that, Glycyrrhizin had affinity to HIV surface proteins.(Julia Hupfeld, et al,2009)

C) Shinji Harada investigated the effect of GL (glycyrrhizin), on the fluidity of the plasma membrane and viral envelope. This study reported the inhibition of viral infection by GL and showed it to be due to suppression of the fluidity of the plasma

membrane and viral envelope into which GL was incorporated. He also reported that its effects on fluidity were readily reversible when GL was withdrawn from the cultures. This study proposed a new anti-viral strategy to directly suppress the fluidity of lipid bilayer membranes, inhibiting the formation of fusion pores, as one of the host factors important for controlling enveloped viral entry. (Shinji Harada,2005)

14) Review on different viruses

Fiore C, et al stated that, glycyrrhizin and its derivatives reduced hepatocellular damage in chronic hepatitis B and C., and has also mentioned that in hepatitis C virus-induced cirrhosis the risk of hepatocellular carcinoma was reduced. In the animal studies, they have further observed that there was reduction of mortality and viral activity in herpes simplex virus encephalitis and influenza A virus pneumonia.

These researchers concluded from the in vitro studies that glycyrrhizin had antiviral activity against HIV-1, SARS related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus and vesicular stomatitis virus. They have summarized the mechanisms for antiviral activity of *Glycyrrhiza glabra* as reduced transport to the membrane and sialylation of hepatitis B virus surface antigen, reduction of membrane fluidity leading to inhibition of fusion of the viral membrane of HIV-1 with the cell, induction of interferon gamma in T-cells, inhibition of phosphorylating enzymes in vesicular stomatitis virus infection and reduction of viral latency.(Fiore C, et al,2008)

The aim of this review was to state the scope of *Glycyrrhiza glabra* as an antiviral agent. In recent years, because of emergence of resistant strains, the focus of drug

manufacturers is on herbal compounds. Ayurveda has been using these compounds for centuries. It is evident from the data of the research in last decade, from the in vitro and in vivo studies that *Glycyrrhiza glabra* has many bioactive compounds such as 18 β -glycyrrhetic acid, Glycyrrhiza aqueous extract, Glycyrrhizin, biochanin B, glabrone, etc which have shown promising antiviral activity against many viruses. As demonstrated by the examples included in this review, there is considerable evidence that *Glycyrrhiza glabra* extracts, have the potential to be developed into agents that can be used as preventive or curative antiviral agents.

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