Antiviral Properties of Glycyrrhizic Acid and its Semisynthetic Derivatives

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Abstract: Some natural triterpenes exert a definite antiviral activity on several human viruses. New synthetic derivatives of glycyrrhizic acid (GL) are even more active than the parental molecule. GL can alter the expression of viral genes involved in cell transformation, thus opening a new window for speculating on viral cancerogenesis.

Key Words: Triterpenes, glycyrrhizic acid, anti-viral activity, triterpene derivatives, latent viral infection.

INTRODUCTION

Terpenes are a large and varied class of compounds produced by a wide number of plants and microorganisms [1]. Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers and may be classified by the number of terpene units in the molecule. Triterpenes are formed by three terpene units and are the basis that characterizes the structure of saponins and steroids. Saponins contain a triterpene moiety and one or more sugar chains in their structure. The chemistry and biological activity of natural saponins are presented in an updated review by Guçlu-Ustundag & Mazza [2].

1. GLYCYRRHIZIC ACID

Glycyrrhizic acid (GL), shown in Fig. (**1**), is a natural saponin, known to be endowed with very low toxicity in both *in vitro* and *in vivo* models. It is a conjugate of 1 molecule of a triterpene and 2 molecules of glucuronic acid; the aglycone moiety is known as Glycyrrhetinic acid (GLA). GL is the major bioactive triterpene glycoside of licorice root extracts and possesses a wide range of pharmacological properties (anti-inflammatory, anti-ulcer, anti-allergic, anti-oxidant, anti-tumor, anti-viral, etc.) [2]. Official sources of GL are Glycyrrhiza glabra L. and Glycyrrhiza uralensis (the Leguminosae family). The content of GL in licorice root varies from 2 to 24% of the dry weight. GL is one of the leading natural compounds used in clinical trials on chronic active viral hepatitis and HIV infections (Stronger Neo-Minophagen C preparation, SNMC), and its monoammonium salt (glycyram, tussilinar) is used as an anti-inflammatory and anti-allergy remedy [3]. Dargan & Subak-Sharpe used the hydrophobic triterpenoid structure of GLA as the basis for the design of a family of related compounds and derivatives such as Carbenoxolone (CBX), and Cicloxolone (CCX) [4]. GL and CBX are currently used as mild anti-inflammatory agents in clinical practice; GL is now routinely used in Japan for the treatment of chronic viral hepatitis [5] and has the capacity of lowering hepatic transaminase release [6]. GL is also endowed with several pharmacological activities, including anti-inflammatory and neuroprotective effects [6, 7].

1.1. Anti-Viral Activity

GL inhibits the growth and cytopathology of several unrelated DNA and RNA viruses, but does not affect cell activity and ability to replicate [8]. In addition, GL inactivates Herpes simplex virus particles irreversibly. This drug completely inhibits both the growth and cytopathic effect of Vaccinia (VV), Herpes simplex type 1 (HSV1), Newcastle disease (NDV) and Vesicular stomatitis viruses (VSV). On the other hand GL has no effect on Poliovirus type 1. GL also produces the irreversible inactivation of infectious Herpes simplex type 1, when incubated at 37° for 15 min at concentrations between 2 and 8 mM [8]. Drug treatment starting 4 h after infection, when the synthesis of virus macromolecules is in progress, still inhibits virus growth completely, while only reducing the extent of the cytopathic effect [8, 9]. GL also shows some peculiar antiviral properties. It can enter the cells and inactivate intracellular HSV1 particles and does not injure the host cells. Its action is irreversible, unlike that of heparin. It does not disrupt the virions, since the buoyant density of viral particles is preserved. The authors conclude that GL can interact with some components of the HSV1 envelope, thus impairing the ability of viral particles to adsorb to new cells [9]. In actual fact, GL inhibits the synthesis of viral glycoproteins, but not that of cell glycoproteins, at concentrations that show a clear antiviral activity. In addition, cell receptor expression for the Fc fragment of IgG (viral glycoprotein E) in HSV1 infected cells is decreased by high concentrations of GL [10]. The drug can exert its antiviral activity by means of two mechanisms: I) at low concentrations, GL specifically inhibits the viral glycoprotein synthesis; II) at higher doses, the drug causes a direct inhibition of the viral infectivity by interacting with the viral envelope.

GL has a synergistic effect with prostaglandin A1 on the inhibition of Vaccinia virus replication in L929 cells [11]. The combination of GL with some physiological proteins such as lactoferrin and lysozyme, even at concentrations usually present in some body fluids, gives significant results in enhancing the antagonistic activity on HSV1 in *in vitro* assays [12]. GL is also capable of inhibiting Influenza A virus replication in embryonated eggs [13]. This drug has no effect on viral viability and does not impair the hemaggluti-

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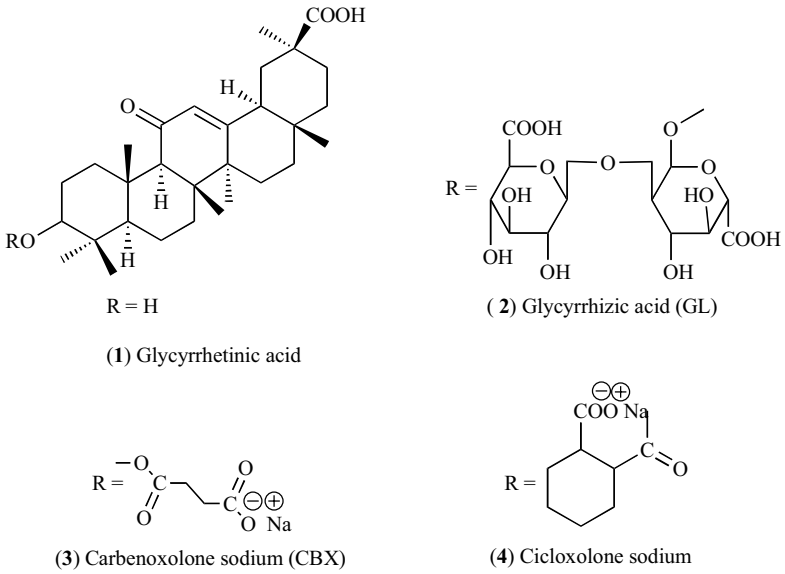

Fig. (1). Structures of Glycyrrhetinic acid and some triterpenic analogs.

nating activity of the virions, suggesting that the growth of viruses in the embryo tissues can be mainly affected. The Newcastle disease virus is inhibited, although to a lower extent, in the embryonated egg model. The activity of GL against HIV and hepatitis A and B viruses has also been described [14-17].

1.2. Activity of the GL aglycone (Glycyrrhetinic Acid)

GLA (**1**), the aglycone form of GL, is more toxic on cell cultures than GL and is also less active on virus inhibition. This probably means that the diglucuronide moiety of GL plays an important role in its inhibitory activity observed on several viruses [9].

1.3. Other Biological Activities of GL

Several other biological properties have been described for GL. Abe *et al*. [18] claimed that GL and GLA had the ability to induce the production of gamma interferon (IFNγ) in mice. This induction may be followed by the activation of macrophages and augmentation of NK activity through the action of the induced INF. Vapaatalo *et al*. [19] described an inhibitory activity of GL on the prostaglandin synthesis. On the other hand, some toxic effects of GL were also described by Mantovani *et al*. [20], who claimed a teratogenic property of GL in rats.

The biological and pharmacological effects of GL have recently been reported in detailed reviews [3, 21].

2. CARBENOXOLONE AND CICLOXOLONE

Carbenoxolone sodium (CBX) and cicloxolone sodium (CCX), the semi-synthetic derivatives of GL shown in Fig. (**1**), were extensively investigated by Dargan & Subak-Sharpe, for general antiviral and particularly for anti-Herpes activity [22-27]. *In vitro*, the rate of cell growth was reduced and the drugs exhibited cytotoxicity only at high concentrations. The presence of CBX and CCX during the Herpes simplex replication reduced the virus yield by 3-4 logs. The drugs appeared to be continuously active throughout the virus multiplication cycle. CCX and CBX greatly diminished the progeny virus quality and infectivity [22]. Dose-response experiments showed that the presence of non toxic doses of CCX or CBX during the HSV replication cycle reduced the infectious virus yield by up to more than 4 logs: CCX was the more potent anti-herpes agent tested in these studies. Both drugs inhibited HSV-2 replication more severely than HSV-1 replication. CCX, and to a lesser extent CBX, can be cytotoxic at high doses, but the degree of cytotoxicity varies on different cell lines. These triterpenoid drugs exhibited some direct activity against virus particles, but this was limited and only provided a minor contribution to the overall antiviral effect. In contrast to most other anti-herpesvirus agents in clinical use, the triterpenoid compounds do not appear to act directly in blocking virus DNA synthesis. HSV growth in the presence of the drugs resulted in a lower number of virus particles, but reduced the infectious virus yield to a much greater extent: thus the progeny virus quality was greatly diminished. SDS-PAGE analysis of the structural proteins of virus particles formed in cells treated with CCX revealed that some polypeptides were synthesized in reduced amounts and the post-translational processing by glycosylation and sulphation of both cellular and HSV induced proteins was strongly inhibited by the triterpenoid drugs [22].

The effect of CBX and CCX on DNA and protein synthesis in uninfected and HSV-infected BHK-21 or Flow 2002 cells was studied [18]. No significant effect of CBX or CCX on HSV DNA synthesis was identified. The synthesis of several HSV proteins was much reduced by treatment with CBX or CCX and the transport of certain proteins between the nuclear and cytoplasmic compartments of infected cells was also affected. CCX treatment of Flow 2002 cells induced the synthesis of several new polypeptides, some of which had the same molecular weights as identified by Flow 2002 cell stress proteins. When treated with high concentrations of CCX, the plasma membranes of both uninfected and HSV-infected cells became increasingly leaky. These results indicated that the antiviral activity of the triterpenoid drugs

was non-specific and acted by interfering with or changing the normal function of cell membranes so that cells could no longer efficiently assemble the virus components into infectious particles, although retaining their viability. The anti-herpes activity of CCX could be partially explained by damage to the envelopment, but in addition, specific effects on other virion tegument proteins might be involved [24]. The same authors suggested that the gene locations encoding gH and gC glycoproteins determined the CCX sensitivity difference between HSV type 1 and type 2 [25]. CCX also reduced the number of VSV particles assembled and released by 2-3 logs. The reduced number of virus particles resulted from the suppression of VSV secondary transcription and viral protein synthesis, and perturbation of virion assembly. CCX also possessed a virucidal effect on mature infectious VSV particles in suspension [26]. The effect of CCX on the replication of different virus families, such as adenovirus type 5 (Ad-5), reovirus type 3 (Reo-3), Bunyamwera and Germiston viruses, poliovirus type 1 (Polio-1) and Semliki Forest virus (SFV), in tissue culture was investigated [27]. Inhibition of glycoprotein processing was responsible for the antiviral activity on some of these viruses.

The authors concluded that the antiviral effect of these molecules could be manifested in three ways: (a) reduction in the virus particle yield in Herpes-viruses and VSV; (b) loss of virion quality and infectivity in Reo-virus; (c) virucidal effect of the drug in the Adeno-virus. In the case of SFV, none of these mechanisms were in operation, but a relocation of the assembled virus was found.

CBX is also known to produce a marked and dose-related inhibition of ethanol-induced gastric lesions in rats. This cytoprotective action is inhibited progressively and significantly by increasing doses of indometacin. This finding confirms previous suggestions that prostaglandins can be involved in the cytoprotective action of CBX [28].

3. NEW SEMISYNTHETIC GL DERIVATIVES

Recently Kondratenko *et al.* [29] started a program of synthesis of GL derivatives by the substitution of diglucuronide moiety of GL with other sugars, such as α-D-glucosamine and some glycosylamines, as shown in Fig. (**2**). These glycoconjugates exhibited antiviral activity towards HSV type 1 virus in an *in vitro* model. Some of the derivatives also demonstrated anti-HIV activity in an *in vitro* test with MT-cells. Compound (**7**) had a low cytotoxicity in the VERO cells and exhibited pronounced antiviral activity towards HSV1. The anti-HIV properties of compounds (**7**) and (**8**) were also estimated. These compounds did not protect the infected cells from death, but induced a marked inhibition of p24 capsidic protein.

After Cinatl *et al.* [30] demonstrated that GL inhibited SARS-coronavirus (SARS-CoV) replication *in vitro*, Hoever *et al*. [31] studied the anti-SARS-CoV effect of 2-acetamido-β-D-glucopyranosylamine GL derivatives and also several other newly synthesized compounds, some of which are shown in Fig. (**3**). Some derivatives inhibited SARS-CoV replication at lower concentrations compared to GL. The introduction of *N*-acetylglycosamine into the glycoside chain of GL as in compound (**7**) of Fig. (**2**), increased the anti SARS-CoV activity about 9 times compared to GL. This compound was found to be extremely well tolerated by the cell cultures *in vitro*, with a resulting high selectivity index. The authors claimed that the introduction of *N*-acetylglucosamine residues into the carbohydrate part of the GL molecule will increase its hydrophilic properties. The highly glycosylated spike-protein of Coronaviruses has been shown to be important for viral entry into the cells by binding to cellular receptors. It was hypothesized that viral entry is inhibited by the binding of *N*-acetylglycosamine to the carbohydrates of the spike-proteins. Other semisynthetic compounds such as (**10**) and (**11**)**,** were active against SARS-CoV, but resulted in high cytotoxicity compared to GL. This means that the chemical modification of GL by the introduction of CONH bonds into the GL molecule might increase its anti-SARS-CoV activity as well as cytotoxicity. The anti SARS-CoV activity of several GL glycopeptides was also tested. Compound (**9**) of Fig. (**3**) was 10-fold more active against SARS-CoV as compared to GL. Amides of GL and conjugates of GL with two amino acid residues and a free -COOH group presented up to 70-fold increased activity against SARS-CoV, but also increased cytotoxicity resulting in lower selectivity index. In contrast, other glycopeptides, which contained glycine, valine, leucine, alanine and glycine-valine,

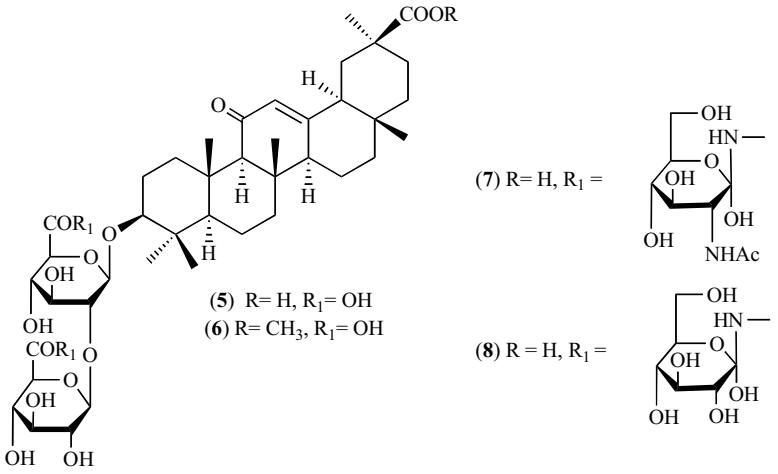

Fig. (2). Glycosylated derivatives of Glycyrrhizic acid.

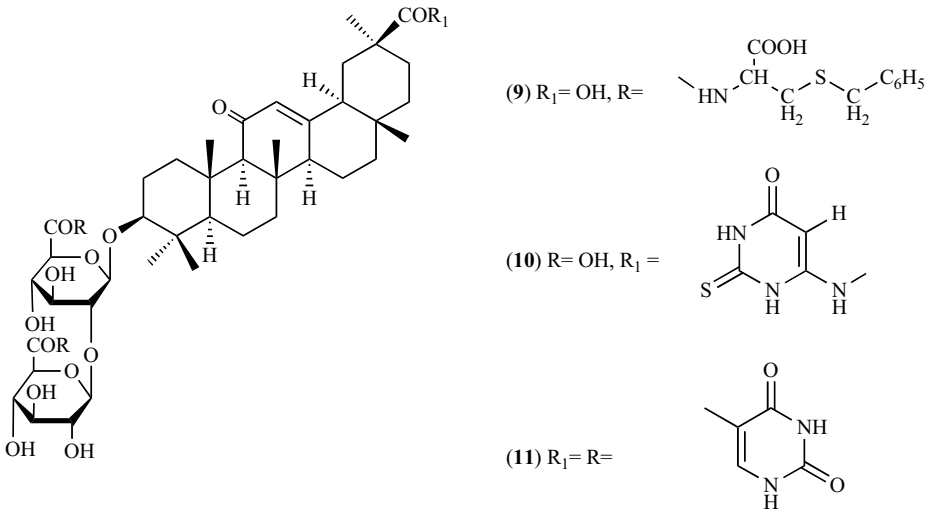

Fig. (3). Glycopeptides and other derivatives of Glycyrrhizic acid.

were inactive against SARS-CoV. This finding shows that the intact -COOH function of GL seems to be important for the anti SARS-CoV activity of GL glycopeptides. In some compounds where the two units of glucuronic acid were replaced with non-carbohydrate functional groups, no anti-SARS-CoV activity was observed [31]. This indicates that the sugar moiety is essential for anti SARS-CoV activity. The conclusion was that modification of GL on the diglucuronic moiety might lead to more potent anti-SARS-CoV drugs.

In summary, the possibility of synthesizing new more active and less toxic GL derivatives, such as new glycosylated triterpenes, provides the chance of preparing very potent and safe drugs able to inhibit a great variety of virus-induced human diseases.

4. ACTIVITY OF GLYCYRRHIZIC ACID ON LATENT HERPESVIRUS

Several compounds able to inhibit herpesvirus infections have been described so far, but they are incapable of altering latent herpesvirus infection. The factors needed for maintaining the virus in its latent state must be blocked, in order to cure a latent herpesvirus infection from infected cells. Curreli *et al*. [32] showed that latent infection with Kaposi sarcoma associated Herpesvirus (KSHV) in B lymphocytes can be terminated by GL. GL was claimed to disrupt latent KSHV infection by down regulating the expression of latency-associated nuclear antigen (LANA) and upregulating the expression of viral cyclin, thus selectively inducing cell death of KSHV-infected cells. Since latent genes are known to be involved in KSHV-induced cell transformation, the possibility of blocking their production and function might help in the eradication of latent KSHV infection. GL treatment of cells infected with Herpes simplex virus 1 was known to reduce the infectious viral yield and was also shown to be effective against Herpes simplex virus 2, Varicella zoster, HHV-6, HHV-7, HHV-8, human CMV and EBV [33-37]. In their study Curreli *et al*. demonstrated that GL selectively promoted cell death in latent KSHV–infected cells, and was not toxic at active concentrations. These results suggested that the presence of KSHV in its latent state makes the cells susceptible to apoptosis when treated with GL and that the change in the expression patterns of LANA and v-cyclin was responsible for the apoptotic effects. Indeed, though less crucial than LANA, an over expressed v-cyclin/cdk6 complex might contribute in inducing apoptosis in KSHV-infected cells.

The authors concluded that the active concentration of GL needed to obtain these results might be considered too high to be used as an antiviral compound, but the discovery of new compounds that inhibit the expression of genes required to maintain latency, hopefully offers a novel strategy for controlling latent viral infections.

5. FUTURE PROSPECTS AND CONCLUSIONS

Triterpenes are among the most studied natural compounds. Since they display such plentiful biological activity, they have been proposed for treating many inflammatory and infectious viral diseases [1, 2, 6, 33]. GL is certainly the most studied of the triterpene derivatives. From 1953 to date, Pub-Med has reported several hundreds of papers dealing with this compound, and scientific interest continues to rise. In 2007 alone, about 60 papers were published and more than 30 appeared in the first half of 2008. The success of GL and its analogs is due to the versatility of their use and the lack of toxicity. Moreover, many semi-synthetic derivatives with improved properties have been made, giving a new impulse to the study and the possible application of these compounds in antiviral chemotherapy. Although triterpene derivatives are active in inhibiting several pathogenic viruses both *in vitro* and *in vivo*, no definite mechanism of action has been discovered to date. This probably means that GL and its derivatives can exert a broad-spectrum antiviral activity mainly by a cytoprotective effect, rather than by a specific inhibition of some viral function. This hypothesis was advanced by some authors and is supported by several reports [11,12,14,18, 24, 27, 37]. We believe that one future field of interest in the study of the biological and antiviral properties of GL and its derivatives will be the speculation of the mechanisms that make the triterpene-treated cells more resistant to several infectious agents.

Finally, the finding that GL can inhibit the gene expression of latent carcinogenic viruses poses new light on the understanding and hopefully the treatment of severe and cure-less chronic viral diseases, such as Kaposi sarcoma and possibly other latent herpes infections [32, 34].

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ABBREVIATIONS

GL	=	Glycyrrhizic acid;
GLA	=	Glycyrrhetinic acid;
CBX	=	Carbenoxolone sodium salt;
CCX	=	Cicloxolone sodium salt;
NK activity	=	Natural killer cell activity;
SDS-PAGE	=	Sodium dodecilsulphate-polyacrilamide gel electrophoresis;
CMV	=	Cytomegalovirus;
EBV	=	Epstein-Barr virus
HHV-6	=	Human Herpesvirus 6
HHV-7	=	Human Herpesvirus 7
HHV-8	=	Human Herpesvirus 8
gH and gC	=	Herpesvirus glycoproteins H and C
p24	=	HIV capsid protein 24

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