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Review article

Ginseng, the natural effectual antiviral: Protective effects of Korean Red Ginseng against viral infection

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ABSTRACT

Korean Red Ginseng (KRG) is a heat-processed ginseng developed by the repeated steaming and air-drying of fresh ginseng. Compared with fresh ginseng, KRG has been shown to possess greater pharmacological activities and stability because of changes that occur in its chemical constituents during the steaming process. In addition to anticancer, anti-inflammatory, and immune-modulatory activities, KRG and its purified components have also been shown to possess protective effects against microbial infections. Here, we summarize the current knowledge on the properties of KRG and its components on infections with human pathogenic viruses such as respiratory syncytial virus, rhinovirus, influenza virus, human immunodeficiency virus, human herpes virus, hepatitis virus, norovirus, rotavirus, enterovirus, and coxsackievirus. Additionally, the therapeutic potential of KRG as an antiviral and vaccine adjuvant is discussed.

1. Introduction

Viruses are infective obligate parasites that can replicate only in the living cells of animals, plants, fungi, or bacteria. Although extremely small in size and simple in structure, viruses cause numerous diseases such as cancer, autoimmune disease, and immunodeficiency as well as organ-specific infectious diseases including the common cold, influenza, diarrhea, hepatitis, etc. [1–4].

Recent progress in the formulation of antiviral therapies and vaccines has helped to prevent, shorten the duration, or decrease the severity of viral infection [5–7]. Most antiviral agents are designed to target viral components, but mutations in the viral genome often result in drug resistance and immune evasion, creating a major hurdle for antiviral therapies and vaccine development [8]. In addition, the continuous emergence of new infectious agents such as the Ebola virus and Middle East respiratory syndrome coronavirus (MERS-CoV) necessitate the advancement of novel therapeutic approaches. Accordingly, great attention has recently been drawn to the development of antivirals with broad-spectrum efficacy and immunomodulators which improve host resilience by increasing host resistance to the viral infection [9].

Korean ginseng (the root of *Panax ginseng* Meyer) is one of the most popular medicinal plants used in traditional medicine in East Asian countries including Korea [10]. Ginseng contains various pharmacologically active substances such as ginsenosides, polysaccharides, polyacetylenes, phytosterols, and essential oils, and among those, ginsenosides are considered the major bioactive compounds [11]. Korean Red Ginseng (KRG) is a heat-processed ginseng which is prepared by the repeated process of steaming and air-drying fresh ginseng [12]. KRG has been shown to possess enhanced pharmacological activities and stability compared with fresh ginseng because of changes in its chemical constituents such as ginsenosides Rg2, Rg3 Rh1, and Rh2, which occur during the steaming process [13].

Currently, numerous studies have reported the beneficial effects of KRG on diverse diseases such as cancer, immune system disorder, neuronal disease, and cardiovascular disease [14–17]. In addition, KRG and its purified components have also been shown to possess protective activities against microbial infections [18]. In this review, we summarize the current knowledge on the effects of KRG and its components on infections with human pathogenic viruses and discuss the therapeutic potential of KRG as an antiviral and vaccine adjuvant.

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2. Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection. This viral infection shows mild and indistinguishable symptoms from common colds in adults and healthy children but can also cause severe lower respiratory tract diseases such as pneumonia and bronchiolitis in premature babies and infants with underlying health conditions and immunocompromised patients. No effective antiviral therapy or preventive vaccine in early life is currently available, but maternal vaccination is considered a possible strategy to provide RSV antibody protection to young infants [1].

The Kang Laboratory (Georgia State University, GA) has published several studies on the immunomodulatory and antiviral effects of KRG extract (RGE) on RSV [19–21]. Although a formalin-inactivated RSV (FI-RSV) vaccine was developed in the 1960s, immunization with FI-RSV was halted because vaccinated children experienced severe respiratory disease during the natural RSV infection. The severe form of the disease caused by the FI-RSV has been attributed to the strong T-helper type 2 (Th2) immune response, and RGE has been shown to mitigate such Th2 responses by enhancing the T-helper type 1 (Th1) response in F1-RSV immunized mice which have Th2-dominant immune response intrinsically [19]. Thus, RGE-treated mice that were immunized with FI-RSV showed improved clinical outcomes via an increase in the immunoglobulin G2a (IgG2a) antibodies level and interferon (IFN)-γ production accompanied by a decrease in IL-4 production and weight loss after RSV infection [19]. The data indicate that RGE possesses an immunomodulatory effect by balancing Th1 and Th2 immune responses, and protects the host from severe pulmonary inflammation upon FI-RSV immunization and RSV infection.

In addition, RGE protected human epithelial cells from RSV-induced cell death and viral replication and inhibited the production of proinflammatory cytokines *in vitro* upon RSV infection [20,21]. Moreover, RGE treatment improved clinical outcomes by preventing weight loss and increasing viral clearance and IFN-γ production in bronchoalveolar lavage cells in mice [20,21]. RGE also increased the numbers of CD11c+ dendritic cells, IFN-γ-secreting CD8+ T cells, and CD4+ T cells in bronchoalveolar lavage fluids [20,21]. Taken together, these studies demonstrate that ginseng has immunomodulatory and antiviral effects against RSV infection through multiple mechanisms, and further studies are required to elucidate the underlying immunoregulatory and antiviral mechanisms at the molecular level.

3. Rhinovirus

Rhinovirus is the major cause of the common cold. Rhinovirus is transmitted from person-to-person via contact or aerosol and causes upper respiratory illness [22]. Although generally mild and self-limiting, rhinovirus infection may cause asthma or chronic obstructive pulmonary disease in chronic infection and lead to severe complications for asthmatics, elderly people, and immunocompromised patients [23,24]. Currently there is no cure or prevention for rhinovirus infection, and treatment mainly relies on symptom alleviation using nonsteroidal anti-inflammatory drugs (NSAIDs), nasal decongestants, and antihistamines. Nonetheless, consistent effort has been made to identify effective preventions and antiviral medication for rhinovirus [25].

In an attempt to investigate the effects of ginsenosides on rhinovirus infection, Song et al [26] examined the antiviral activities of protopanaxatriol (PT)-type ginsenosides (Re, Rf, and Rg2), and protopanaxadiol (PD)-type ginsenosides (Rb1, Rb2, Rc, and Rd). The results showed that PT-type ginsenosides protected HeLa cells from human rhinovirus 3 (HRV3)-induced cell death as determined by sulforhodamine B staining of viable cells and morphological assessment [26]. However, PD-type ginsenosides did not show any protective effects and even stimulated the HRV3-induced cell death significantly, implying a structure-dependent effect of ginsenosides on HRV3. The selective antiviral activities of panaxatriol-type ginsenosides were also found in the case of coxsackievirus, as described below. Future studies are needed to elucidate the relationship between the antiviral activities and structural differences among panaxadiol- and panaxatriol-type ginsenosides.

4. Influenza virus

Influenza virus is the most common human respiratory pathogen that causes annual endemic and periodic pandemic infection. There are three types of influenza viruses: A, B, and C. Human influenza A and B viruses cause seasonal disease nearly every winter, whereas the influenza C virus causes mild respiratory disease. Influenza A viruses are the most virulent human pathogens, and their serotypes are further classified and termed based on the viral surface proteins hemagglutinin (H) and neuraminidase (N). Novel mutant strains continuously emerge causing influenza pandemic outbreaks, and there were some historically renowned lethal strains such as “Spanish influenza (H1N1)”, “Asian influenza (H2N2)”, “Russian influenza (H1N1)”, “Hong Kong influenza (H5N1)”, and swine-origin H1N1 influenza recently found in Mexico [27,28].

Ample studies have been conducted to demonstrate the antiviral activities of RGE and purified compounds present in ginseng on influenza virus A infection *in vitro* and *in vivo*. RGE treatment improved the viability of human alveolar epithelial A549 cells upon H1N1 infection accompanied by a decrease in virus-induced cytokine secretion and reactive oxygen species (ROS) formation [29]. Protopanaxatriol-type ginsenoside Re has been shown to protect human umbilical vein endothelial cells (HUVECs) from avian H9N2/G1 influenza-induced apoptosis by inhibiting virus-induced interferon-inducible protein-10 (IP-10) production [30]. The inhibitory effects of RGE on viral replication were also tested in Madin–Darby canine kidney (MDCK) cells using the 2009 pandemic H1N1 virus [31]. In *in vivo* studies, RGE, ginseng polysaccharide (GP), or ginseng saponin was orally administered to mice or ferrets prior to viral infection, and their protective effects were evaluated by measuring body weight, survival rate, lung viral titers, cytokine production, histopathology, etc. The antiviral effects on the H1N1 strain have been most widely tested, and those on H3N2, H9N2/G1 (avian influenza), and H5N1 were also examined. In detail, RGE has been reported to have antiviral effects on H1N1, H3N2, and H5N1 [31,32]; GP has effects on H1N1 and H3N2 [33]; and saponin has an effect on H1N1 [34]. The antiviral activities of RGE, GP, and ginseng saponin fraction have also been compared using the H1N1 strain. Yin et al [34] showed that GP was the most effective in improving the symptoms of influenza virus infection, followed by RGE and saponin in that order.

In addition to antiviral activity, RGE also plays a role as a mucosal adjuvant against influenza virus A/PR8 during viral infection [35]. When administered with inactivated virus and RGE intranasally, immunized mice produced increased levels of influenza virus-specific antibodies with improved neutralizing activities in blood and mucosal secretions, notably the IgA antibody in the lung. RGE plus virus immunization also resulted in the enhanced secretion of Th1 and Th2-type cytokines in splenocytes upon challenge infection, although a Th2 type response was more remarkable. This adjuvant effect of RGE was comparable to that of conventional adjuvants such as aluminum hydroxide and cholera toxin. Additionally, immunization of mice with inactivated H3N2 influenza antigen and ginsenoside Re resulted in increased immune

responses by elevating both Th1 and Th2 cell activities [2]. The secretion of serum-specific IgG1 and IgG2a and hemagglutination inhibition titers were all increased, and *in vitro* stimulation of splenocytes produced higher levels of Th1 and Th2 cytokines in ginsenoside Re-administered mice. Furthermore, dietary intake of RGE and Korean Red Ginseng saponin (KRGS) has also been shown to improve H1N1 vaccine efficacy by increasing anti-influenza virus A-specific IgG titers and survival rates [36]. In addition, GP induced cross-protective vaccine efficacy. When mice were vaccinated with influenza virus-like particles (VLPs) originating from H1N1 together with GP, the immunized mice developed heterosubtypic protection and survived a lethal challenge with the H3N2 virus. Taken together, the data suggest the use of RGE, KRGS, ginsenoside Re, and GP as adjuvant or dietary supplements to enhance the vaccine-induced immune response and improve protection against influenza virus infection.

5. Human immunodeficiency virus

Human immunodeficiency virus (HIV) belongs to the genus *Lentivirus* in the family Retroviridae, and two types of HIV have been characterized: HIV-1 and HIV-2 [37]. HIV-1 is the major type of HIV accounting for 95% of infections worldwide and is more virulent and infectious than HIV-2 [38]. HIV-2 is mainly seen in West Africa and has lower infectivity [39,40]. There are well-defined stages of HIV disease progression from acute infection, clinical latency, and acquired immunodeficiency syndrome AIDS, and an HIV-positive patient is diagnosed with AIDS when his/her CD4+ cell count falls < 200 cells/mm^3. HIV treatment or highly active antiretroviral therapy (HAART) involves the combination of multiple drugs with different mechanisms of action. HAART can effectively suspend or prevent disease progression from one stage to the next and prolong the lives of HIV-positive patients dramatically by lowering the viral load, maintaining immune system function, and preventing opportunistic infections [7,41]

When combined with zidovudine monotherapy or HAART, RGE has been shown to exert antiviral effects by maintaining CD4+ T cell counts [42–45] and delaying the occurrence of resistance mutation [42,43,46] in HIV-1 patients. RGE treatment alone even showed significant antiHIV effects [44,47–49], implying that RGE intake may become an alternative form of treatment for HIV-1 patients. Negative factor (Nef) is a virulence factor required for achieving high virus load and the progression to AIDS [50]. The 5′ long terminal repeat (LTR) acts as a promoter of the entire viral genome and stimulates viral genome replication, whereas group-specific antigen (gag) promotes the formation of fully infectious HIV-1 virions. Interestingly, RGE intake increases the frequency of gross deletions in Nef genes [51–54] and the 5′ LTR/gag gene [53,55,56], leading to a delay in disease progression and increase of survival rate in HIV-1 patients.

Although most studies evaluating the effects of ginseng on HIV-1 have been carried out in HIV-1 patients, several *in vitro* studies have also been performed. For example, a homodimeric protein, quinqueginsin, isolated from the roots of American ginseng *Panax quinquefolium*, and xylanase, isolated from the roots of *Panax notoginseng*, have been shown to inhibit reverse transcriptase in a cell-free system [57,58]. Additionally, ginsenoside Rh1, ginsenoside Rb1, and compound K have been reported to inhibit cytoprotective effects which may contribute to the long-term survival and persistent HIV-1 production in cells constitutively expressing transactivator (Tat) proteins [59–61].

In addition to antiviral effects, ginseng interacts with antiHIV drugs and changes their pharmacokinetic properties. Shi et al [62] have reported that ginsenoside Rh2 increased the accumulation and decreased the efflux of ritonavir through P-glycoprotein (P-gp) in Caco-2 cells and MDCK-MDR1 cells. An *in vivo* study using rats confirmed that intravenous administration of ginsenoside Rh2 inhibited ritonavir efflux and increased the plasma level of ritonavir. However, American ginseng, *Panax quinquefolium,* did not affect the pharmacokinetics of an antiHIV drug cotreated in humans, although it induced phase 2 enzyme quinone reductase [63]. Kaempferol isolated from ginseng has also been reported to inhibit P-gp-mediated efflux of ritonavir and cytochrome P-450 3A4 (CYP3A4) activities *in vitro* [64], but it has not been confirmed whether kaempferol would indeed induce the level of ritonavir *in vivo*.

6. Human herpesvirus

The herpesviruses are a group of large DNA viruses causing lytic, persistent, and latent/recurrent infections [65]. The human herpesviruses (HHV) are further divided into three subfamilies, alphaherpesvirinae [including herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), and varicella-zoster virus (VZV)], betaherpesvirinae, and gammaherpesvirinae based on the differences in factors such as tissue tropism, pathogenesis, and site of latent infection [66]. HSV-1 is typically transmitted during childhood by contact with infected skin and is associated with orofacial infections and encephalitis [67,68], although HSV-2 is transmitted by sexual activity and causes genital herpes mostly [68].

Notoginsenoside ST-4 is a dammarane-type saponin of *Panax notoginseng* and has been reported to show antiHSV activity by inhibiting the penetration of HSV-1 into Vero cells [69]. Another *in vitro* study has shown that ginsenoside Rb1 promotes cell proliferation and inhibits the apoptosis of human glioma cells upon HSV infection, suggesting the potential application of ginsenoside Rb1 to prevent neuronal cell death in viral encephalitis [70]. The antiHSV-1 activity of RGE has also been reported *in vivo*. When Balb/c mice were administered 200 mg/kg or 400 mg/kg of RGE orally for 10 days and infected with HSV-1, the RGE-treated mice became more resistant to vaginal and systemic infection as shown by a decrease in clinical severity and increase in survival rate and viral clearance. RGE also stimulated IFN-γ secretion in vaginal lavage fluid and increased the expression of IFN-γ, granzyme B, and Fas-Ligand mRNA in lymph nodes and vaginal tissue, suggesting that RGE protects the host from HSV-1 infection by stimulating natural killer (NK) cell activities [71]. Given the diverse antiviral activities of RGE through the inhibition of viral penetration and cell death and NK cell activation, prophylactic use of RGE would be beneficial for preventing or alleviating primary and recurrent HSV infection in combination with conventional antiviral drugs [72].

7. Hepatitis A virus

Hepatitis A virus (HAV) is a positive-sense, single-stranded RNA virus, belonging to the family Picornaviridae. Unlike hepatitis B virus (HBV), which is transmitted through exposure to blood and various body fluids of infected people, HAV is largely transmitted by the fecal–oral route and causes acute hepatitis. Although hepatitis A infection does not lead to chronic liver disease and has very low mortality, it may cause enervating symptoms and fulminant hepatitis (acute liver failure) [4]. Currently, no specific antiviral agent is available for HAV, and thus, prevention via vaccination and improvement of hygiene and sanitation is the most effective approach against the HAV infection.

Lee et al [73] examined the antiviral effects of RGE and purified ginsenosides Rb1 and Rg1 against HAV infection. They demonstrated that pretreatment or cotreatment with RGE and ginsenosides Rb1 and Rg1 on FRhK-4 cells derived from the monkey kidney decreased the HAV titer upon HAV infection *in vitro*. Although the

antiviral effect of RGE and ginsenosides remained limited to the *in vitro* model, the report suggested that regular intake of KRG as a dietary supplement may help prevent HAV infection.

8. Hepatitis B virus

Hepatitis B virus (HBV) is a double-stranded DNA virus classified as being in the family Hepadnaviridae [74]. HBV can cause acute hepatitis, but it can also develop into a long-term, chronic infection. As chronic hepatitis B can lead to life-threatening cirrhosis or hepatocarcinoma, HBV infection is one of the most serious health problems worldwide [75]. During viral replication, large amounts of HBV surface antigen (HBsAg), HBV envelope antigen (HBeAg), and virions are released in the blood, and accordingly, diagnostic tests for HBV infection involve the detection of those viral antigens, virions, and antibodies to the viral antigens.

The antiHBV effect of ginsenoside Rg3 has been well-described [76]. Ginsenoside Rg3 remarkably inhibited the secretion of HBsAg, HBeAg, and viral particles in HBV-infected HepG2.2.15 cells. Another mechanistic study revealed that ginsenoside Rg3 down-regulated TNF receptor-associated factor 6 (TRAF6)/transforming growth factor β activated kinase-1 (TAK1) and inhibited the mitogen-activated protein kinase (MAPK) signaling pathway by impeding c-Jun phosphorylation and reducing AP-1 expression. Consequently, the expression of proinflammatory cytokines such as IL-8 and TNF-α was reduced. Although the anti-inflammatory activity of ginsenoside Rg3 is explicitly described, it is unclear how the anti-inflammatory effect of ginsenoside Rg3 affects HBV replication. Future studies should strive to better understand the link between antiHBV and anti-inflammatory activities of ginsenoside Rg3.

9. Norovirus

Norovirus is a positive-sense, single-stranded RNA virus causing nausea, vomiting, abdominal pain, and diarrhea in humans [77]. The virus is spread through the fecal–oral route by ingestion of contaminated water or food, especially fish and shellfish [78]. As human norovirus is not culturable, norovirus surrogates such as feline calicivirus (FCV), murine norovirus (MNV), and Tulane virus (TV) are used to test the antiviral activity of natural or chemical compounds against norovirus [79]. FCV and MNV have a similar genome organization, physical properties, and replication cycle to those of human norovirus and can be cultivated in Crandell–Reese feline kidney (CRFK) cells and murine Raw264.7 cells, respectively [80].

Lee et al [81] have shown that pretreatment of CRFK or RAW264.7 cells with RGE and ginsenosides Rb1 or Rg1 significantly reduced FCV and MNV titers *in vitro*, whereas cotreatment or posttreatment had no antiviral effects. In a subsequent study, the same research group demonstrated that RGE and ginsenosides pretreatment induced antiviral proteins in FCV-infected CRFK cells. The expressions of IFN-α, IFN-β, IFN-ω, zinc finger antiviral protein shorter isoform (ZAPS), and Mx protein, an IFN-inducible protein with antiviral activity, were all increased which contributed to the decrease of viral titers in CRFK cells. Future studies are needed to establish a culture system for human norovirus and subsequently evaluate the antiviral effects of RGE and ginsenosides against human norovirus.

10. Rotavirus

Rotavirus is the leading cause of acute gastroenteritis in young children age ≤ 5 years [82]. Two live oral rotavirus vaccines (Rotarix by GlaxoSmithKline, Unitied Kingdom, and RotaTeq by Merck, United States) are available, and the implementation of rotavirus vaccines in childhood immunization programs has significantly reduced the morbidity and mortality associated with *Rotavirus* infection [6]. Nevertheless, there is no antiviral drug to treat rotavirus infection, and mostly, therapeutics involve the prevention of dehydration [83,84].

In traditional medicine, ginseng has been known to improve gastrointestinal function and prevent gastrointestinal problems such as diarrhea [3]. A recent study researched the active constituent in ginseng and reported that two pectic polysaccharides isolated from hot water extract of ginseng prevented cell death from viral infection [3]. The polysaccharides, named GP50-dHR and GP50-her, did not have virucidal effects but inhibited viral attachment to the host cells thereby protecting them from virus-induced cell death. Given these results and an additional report that other pectin-type polysaccharides in ginseng inhibited the adherence of *Helicobacter pylori* to gastric epithelial cells and the ability of *Porphyromonas gingivalis* to agglutinate erythrocytes [85], further evaluation of the antimicrobial effects of acidic polysaccharides with the structure of pectin is merited.

11. Enterovirus

Human enterovirus 71 (EV71) and coxsackievirus A16 (CVA16) are the two major causes of hand-foot-and-mouth disease (HFMD) in young children [86]. Although HFMD is a mild and self-limited disease characterized by fever, rash, bumps, blisters, or ulcers in the mouth, feet, hands, and buttocks, some affected children may develop neurological, cardiovascular, and respiratory complications in rare cases [87,88]. Presently, there are no specific treatments or vaccines for HFMD.

In order to identify ginsenosides with antiviral activity against EV71, Song et al [26] tested panaxadiol-type ginsenosides (Rb1, Rb2, Rc, and Rd) and panaxatriol-type ginsenosides (Re, Rf, and Rg2). They found that only ginsenoside Rg2 had antiviral activity against EV71 infection in Vero cells, but it has not been determined whether the anticytopathic effect of Rg2 is due to the virucidal activity or the inhibition of viral attachment.

12. Coxsackievirus

Coxsackievirus is a positive-sense, single-stranded RNA virus, belonging to Picornaviridae. Coxsackieviruses are divided into the group A virus with 23 serotypes and the group B virus with six serotypes [89,90]. Among those, the most common pathogens are coxsackievirus A16 (CVA16) causing HFMD as described above and coxsackievirus B3 (CVB3) causing myocarditis, aseptic meningitis, and pancreatitis [91,92]. At present, there is no effective therapeutic agent against CVB3, and only ribavirin is available for CVB3 infection despite its weak antiviral activity [93].

20(*S*)-Protopanaxtriol is one of the major triterpenes isolated from *Panax notoginseng* [94]. It has been shown that 20(*S*)-protopanaxtriol has potent antiCVB3 activities *in vitro* and *in vivo*. The IC_{50} of 20(*S*)-protopanaxtriol for inhibition of CVB3 replication in HeLa cells was even lower than that of ribavirin, indicating a stronger antiviral effect than ribavirin. *In vivo* experiments showed that treatment of CVB3-infected mice with 20(*S*)-protopanaxtriol significantly improved CVB3-induced myocarditis represented by a decrease in the activities of lactase dehydrogenase and creatine kinase, markers for myocardial injury.

In addition, panaxatriol-type ginsenosides such as ginsenosides Re, Rf, and Rg2 also showed significant antiCVB3 activity represented by a decrease in the CVB3-induced cytopathic effect and an increase in the cell viability of infected Vero cells [26]. The antiCVB3 activity of ginsenosides Re and Rf was comparable to that of

ribavirin. However, panaxadiol-type ginsenosides such as Rb1, Rb2, Rc, and Rd did not exhibit antiCVB3 activity.

13. Conclusion

The swift emergence of new infectious viruses and drug-resistant variants has limited the availability of effective antiviral agents and vaccines. Thus, the development of broad-spectrum antivirals and immunomodulating agents that stimulate host immunity and improve host resilience is essential. Although ginseng itself can exert direct antiviral effects by inhibiting viral attachment, membrane penetration, and replication, the foremost antiviral activities of ginseng are attributed to the enhancement of host immunity. Future studies should include the identification of essential components responsible for the enhanced immunity against any viral attack.

Conflicts of interest

None declared.

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