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Review Article

Antiviral Potential of the Genus *Panax*: An updated review on their effects and underlying mechanism of action

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ABSTRACT

Viral infections are known as one of the major factors causing death. Ginseng is a medicinal plant that demonstrated a wide range of antiviral potential, and saponins are the major bioactive ingredients in the genus *Panax* with vast therapeutic potential. Studies focusing on the antiviral activity of the genus *Panax* plant-derived agents (extracts and saponins) and their mechanisms were identified and summarized, including contributions mainly from January 2016 until January 2022. *P. ginseng*, *P. notoginseng*, and *P. quinquefolius* were included in the review as valuable medicinal herbs against infections with 14 types of viruses. Reports from 9 extracts and 12 bioactive saponins were included, with 6 types of protopanaxadiol (PPD) ginsenosides and 6 types of protopanaxatriol (PPT) ginsenosides. The mechanisms mainly involved the inhibition of viral attachment and replication, the modulation of immune response by regulating signaling pathways, including the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, cystathionine γ-lyase (CSE)/hydrogen sulfide (H_2S) pathway, phosphoinositide-dependent kinase-1 (PDK1)/ protein kinase B (Akt) signaling pathway, c-Jun N-terminal kinase (JNK)/activator protein-1 (AP-1) pathway, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. This review includes detailed information about the mentioned antiviral effects of the genus *Panax* extracts and saponins *in vitro* and *in vivo*, and in human clinical trials, which provides a scientific basis for ginseng as an adjunctive therapeutic drug or nutraceutical.

1. Introduction

Viruses are small and simple agents that reproduce only in living cells and contain only one type of nucleic acid (DNA or RNA). However, viral infections are known as one of the major factors causing death and numerous infectious diseases, such as diarrhea, hepatitis, and the common cold, around the world [1]. Some viruses infect animals and have an impact on socio-economic industries [2]. Currently, vaccination and antiviral agents have provided protection against viral pathogens, which also exert side effects such as drug resistance and genetically linked mutants with ensuing therapeutic failure [3,4]. Therefore, there is an urgent need for novel and efficient drugs to treat challenging viral infections.

The genus *Panax* contains a group of prized medicinal herbs that have a long history and a wide range of applications [5]. Of the 17 *Panax* species, *Panax ginseng* Meyer. (Korean ginseng), *Panax notoginseng* (Burkill) F.H. Chen (Chinese ginseng), and *Panax quinquefolius* L. (American ginseng) are valuable ginseng botanicals [6] against viral infection. The root of *P. ginseng* as traditional medicine

Abbreviations: ARI, acute respiratory illness; BG, black ginseng; BVDV, bovine viral diarrhea virus; CHB, chronic hepatitis B; CSFV, classical swine fever virus; CVBs, group B coxsackieviruses; DAA, direct-acting antiviral therapies; EBV, the Epstein-Barr virus; EV, enterovirus; EV71, human enterovirus 71; GCRV, grass carp reovirus; GSLS, Ginseng stem-leaf saponins; HAART, highly active antiretroviral drug therapy; HBV, hepatitis B virus; HCV, Hepatitis C virus; HIV-1, human immunodeficiency virus type 1; HP, highly pathogenic; HSV, herpes simplex virus; HVJ, hemagglutinating virus of Japan; IFN-1, type-I interferon; JAK, janus kinase; JNK, c-Jun N-terminal kinase; KRG, Korean Red Ginseng; KSHV, Kaposi's sarcoma-associated herpesvirus; MHV-68, murine gammaherpesvirus 68; NDV, Newcastle disease virus; NK, natural killer; PPD, protopanaxadiol; PPT, protopanaxatriol; PNAB, PEGylated nanoparticle albumin-bound; PNR, *P. notoginseng* root water extract; PRRSV, porcine reproductive and respiratory syndrome virus; RSV, respiratory syncytial virus; RV, rotavirus; STAT, signal transducer and activator of transcription.

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Table 1
Saponins or Ginseng Extracts Possessing Antiviral Activity and Their Mechanisms of Action

In vitro/ In vivo /Clinical trials	Saponin/Extract	Cell line used/Animals/ Enrolled subjects	Viruses	Antiviral Activity	Mechanism of Action	Ref.
In vitro	Ginseng Extract	MDCK cells, CHO cells	A/Nanchang/8002/ 2009 H1N1 (NC2)	Reduced the viral titer	Interact with viral hemagglutinin proteins to prevent the attachment of the virus with α 2-3′ sialic acid receptors	[23]
	Ginsenoside Rb1	Rhabdomyosarcoma (RD) cells	EV71 strains SHAPHC695F/SH/CHN/ 10 (695F)	IC_{50} = 0.1495 μM	Reduced EV71-induced viral protein-1 (VP-1) expression	[45]
	Ginsenoside Rb2 Ginsenoside Rb3	MDBK cells	BVDV	EC_{50} = 57.76 μg/mL EC_{50} = 60.25 μg/mL	Inhibition of BVDV replication and proliferation	[87]
	20(R)-ginsenoside Rh2	Vero cells	MHV-68	IC_{50} = 2.77 μM	Inhibition of MHV-68 multiplication	[59]
	Ginsenoside Rg3	Huh7 and Huh7.5.1 cells	HCV	Inhibited HCV propagation and the expression of HCV core protein	Rescued the HCV-induced Drp1-mediated aberrant mitochondrial fission via mitophagy	[76]
		Grass CO epithelial cells	GCRV	Restrained the GCRV virus replication	Promoted immune-related genes in the IFN-I pathway	[78]
		HepG2.2.15 cells	HBV	IC_{50} = 96 μM, inhibiting HBsAg secretion IC_{50} = 89 μM, inhibiting HBeAg secretion	Stimulation of TRAF6/TAK1 degradation and inhibition of JNK/ AP-1 signaling	[71]
		Mouse NIH3T3 fibroblast, Vero, BC-3 and Raji cells	MHV-68	IC_{50} = 25.24 ± 4.42 μM (20(R)-Rg3) IC_{50} = 10.82 ± 1.56 μM (20(S)-Rg3)	Inhibition of MHV-68 lytic replication and viral proliferation by suppressing the p38 and JNK signaling pathways	[61]
		Vero cells	HSV-1, HSV-2	IC_{50} = 35 μM	/	[60]
	Ginsenoside Rg1	Marc-145 cells	PRRSV strains (XH-GD, JXA1, VR2332 and HNLY)	EC_{50} = 75.05 μM (XH-GD) EC_{50} = 71.33 μM (JXA1) EC_{50} = 55.05 μM (VR2332) EC_{50} = 94.21 μM (HNLY)	Reduced mRNA levels of the proinflammatory cytokines and inhibited the activation of the NF-κB signaling pathway	[18]
	Ginsenoside Rg2, Re and Rf	Vero cells	EV71, CVB3 and HRV3	Exhibited significant antiviral activities against EV71, CVB3 and HRV3	/	[46]
	20(S)-protopanaxtriol	HeLa cells	CVB3	IC_{50} = 2.74 μg/ml, inhibition of CVB3 replication	/	[42]
	Korean Red Ginseng Extract (KRGE)	HEp2 and A549 cells	RSV A2 strain	Protected HEp2 cells from RSV-induced cell death	Inhibition of CVB3 replication, the formation of ROS and inflammatory cytokine genes	[90]
		HEp2 and RAW264.7 cells			Inhibition of viral replication and the production of pro-inflammatory cytokines	[91]
		PBMCs, NK cells, BCBL-1 cells	The influenza A virus subtype 1 /H1N1 strain	/	Enhanced the activation of immune cells and repressing viral reactivation to the lytic cycle	[29]
	OCD20015-V009	MDCK and RAW 264.7 cells	Influenza A/PR/8/34 (H1N1) virus	Decreased the virus replication	Stimulation of the antiviral response	[25]
	Panax notoginseng Water Extract	MDCK, YAC-1 and RAW 264.7 cells	Influenza A/PR/8/34 (H1N1) virus, KBPV-VR-32 (H3N2)	Inhibition of viral protein and viral mRNA	Stimulation of pro-inflammatory cytokines and the phosphorylation of type-I IFN-related proteins	[24]
In vivo	Ginsenoside Rb1	BALB/c mice	A/Nanchang/8002/ 2009 H1N1 (NC2)	Resulted in minimal weight loss and complete protection over lethal infection	Interact with viral hemagglutinin proteins to prevent the attachment of virus with α 2-3′ sialic acid receptors	[23]
		two-day-old suckling mice	EV71 strains SHAPHC695F/SH/CHN/ 10 (695F)	The survival rate of Rb1 group was 100%	Reduced EV71-induced viral protein-1 (VP-1) expression and activated innate immunity	[45]
	Ginsenoside-Rb2	BALB/c mice	RV-SA11	Reduced virus titers in the bowels of RV-infected mice	Enhanced the resistance of immature host against RV	[53]
		LLCMK-2 cells, BALB/c mice	HVJ	Protected against the lethal infection of HVJ in mice with a survival rate of 71.4%	Activation of mucosal immune cells	[50]
	Ginsenoside Rg1	piglets	PRRSV JXA1	Protected lung injury, decreased viral load in serum and tissues, and improved survival rate	/	[18]
	20(S)-protopanaxtriol	BALB/c mice	CVB3	Decreased virus titers and pathological changes in the hearts	Inhibition of CVB3 replication and protected against CVB3-induced cardiac injury and inflammatory cell infiltration	[42]
	Korean Red Ginseng Extract (KRGE)	BALB/c mice	RSV A2 strain	lowered lung viral loads Prevented mouse body weight loss	Stimulation of IFN-γ production Stimulation of IFN-γ production and types of immune cells migrating into the lung	[90] [91]
		C57BL/6 wild-type and Gulo(−/−) mice	The influenza A virus subtype 1/H1N1 strain		Inhibition of lung inflammation and pro-inflammatory cytokine	[29]

Table 1 (*continued*)

				Increased the survival and decreased the virus-induced inflammation in Gulo(−/−) mice		
		BALB/c mice, ferrets	HP H5N1 influenza virus A/Vietnam/1203/04 (clade 1)	Protected mice and ferrets from lethal infections by HP H5N1 influenza virus	Induced the IFN-α and -γ antiviral cytokines	[27]
	Fermented Ginseng Extract	Wild-type BALB/c and C57BL6 and mutant mice (CD4 T cell-deficient; CD8 T, B cell and MHCII deficient)	H1N1, H3N2, H5N1, and H7N9 strains	Protected against weight loss with 100% survival rates during primary infection and developed immunity against secondary viral infection	Inhibition of viral replication and lung inflammation	[26]
	Black Ginseng Extract	BALB/c mice	H1N1 (A/California/04/2009) virus	Protected mice from lethal infections	Mediated host innate immune responses by binding of the influenza virus particle	[28]
	Panax notoginseng Water Extract	BALB/c mice	Influenza A/PR/8/34 (H1N1) virus	Decreased mortality and prevented weight loss	Stimulation of NK cell activity	[24]
	Panax notoginseng	BALB/c mice	CVB3	Alleviated myocarditis and decreased the viral mRNA expression	Enhanced the expression of CSE/H_2S pathway	[41]
	Saponins and notoginsenoside R1	Piglets	PRRSV strains (NJGC)	Decrease the incidence and severity of immunopathological damages induced by PRRSV	Strengthened the immune system	[19]
Clinical trials	KRGE	252 HIV-1 patients	HIV-1	Decreased $CD4^+$ T-cell count	/	[34]
		68 HIV-1 patients		Decreased in $CD4^+$ T cells and on serum sCD8 levels		[35]
		46 HIV-1 patients		Lowered high-level resistance mutations		[36]
	KRG powdered capsule	38 CHB patients	HBV	Downregulated the well-correlated marker with fibrosis		[70]
	CVT-E002	198 enrolled subjects, Phase II clinical trials	Influenza and RSV	The overall relative risk of ARI was reduced by 89%		[31]

IC_{50} represents the half maximal inhibitory concentration; EC_{50} represents the half maximal effective concentration.

has been utilized for first aid, health care, and cardiovascular disease in Asian countries for thousands of years [7]. The root of *P. notoginseng*, known as Sanqi or Sanchi in China, originated from ethnic minorities in southwest China approximately 500 years ago [8]. *P. quinquefolium*, grown in North America, has the functions of drug prevention and medical treatment [9]. Ginseng extract contains a series of active phytochemicals, including saponins, polysaccharides, flavonoids, and polyphenols [10]. Ginsenosides are triterpenoid saponins, believed to be the major pharmacologically active ingredients with tremendous antiviral effects in the genus *Panax* [11]. Most known ginsenosides belong to the four-ring dammarane family. Dammarane-type ginsenosides can be classified into two groups according to the positions at which the sugar moiety is attached: the protopanaxadiol (PPD) and protopanaxatriol (PPT) groups [12]. The typical PPD type, including ginsenosides Rb1, Rb2, Rb3, Rh2, and Rg3, has a β-OH attached at C−3 and/or C−20 of the sugar moiety, while the typical PPT type, including ginsenosides Rg1, Rg2, Re and Rh1, has an α-OH attached at C−6 and/or a β-OH attached at C−20 of the sugar moiety (Fig. 1) [10,13].

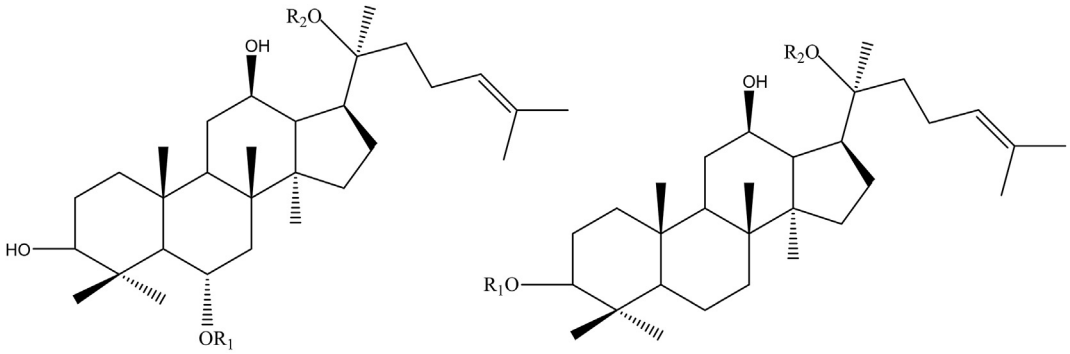
Numerous recent studies have focused on the antiviral activity in genus *Panax* as the emergence of new virus strains, including SARS-CoV-2 and diverse virus mutations. Thus, it is necessary to update the review of research in this field. This review aims to summarize the current knowledge regarding the antiviral capacity and mode of action of the genus *Panax* and their main bioactive saponins (Table 1).

2. Porcine reproductive and respiratory syndrome virus (PRRSV)

PRRS was one of the most epidemic porcine contagious diseases identified in Europe in 1991 [14] and causes massive economic losses in the modern pig industry [15]. PRRSV is the positive-sense RNA virus with a single-strand of the *Arteriviridae* family that causes PRRS [16]. The European genotype and the North American genotype are two well-known PRRSV genotypes [17]. Ginsenoside Rg1 was reported to suppress type 2 PRRSV adhesion, propagation, as well as inflammatory responses by reducing the production of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) and NF-κB signaling pathway in PRRSV-infected Marc-145 cells and porcine alveolar macrophages (PAMs). In addition, Rg1 treatment improved clinical outcomes in 4-week-old piglets by preventing lung injury, decreasing viral load in serum and tissues, and improving the survival rate [18]. Intraperitoneal injection with *P. notoginseng* saponins and notoginsenoside R1 protected against PRRSV-induced immunopathological damage, including elevated weight loss, the body temperature, and anemia in PRRSV-infected piglets. Furthermore, the saponin components strengthened the immune response by upregulating the levels of albumin, IgG, and IgM in PRRSV-infected piglets [19]. These findings could provide a theoretical framework for further research on ginseng as a broad-spectrum anti-PRRSV medicament.

3. Influenza virus

Influenza viruses are enveloped viruses of the *Orthomyxoviridae* family, with antigenic differences in their nucleocapsid and matrix proteins classifying them as A, B, and C [20]. Among them, influenza A virus is the most frequent cause of clinical respiratory pathogen in human, and novel mutant strains such as H7N9, H9N2, H5N1, H3N2, and H1N1 cause annual epidemics [21,22]. Different ginsenosides, including Rb1, Rb2, Rb3, Rg1, PPT, and PPD, have been identified for their role in the 2009 H1N1 pandemic. The ginsenosides protect BALB/c mice from weight loss and mortality, and the representative ginsenoside Rb1 prevented the 2009 pandemic H1N1 influenza virus (2009 pdm H1N1) from entering into the host cells. Mechanistic investigations indicated that ginsenoside Rb1 interacted with viral hemagglutinin protein and blocked the virus from adhering to 2-3′ sialic acid receptors on the cell surfaces. This interaction requires sugar motifs attached to a ginsenoside backbone, and the lack of sugar motifs resulted in the absence of



PPT-type:

Name	R_1	R_2
protopanaxatriol	H	H
Ginsenoside-Rg1	Glc-	Glc-
Ginsenoside-Re	Rha^1-^{2}Glc-	Glc-
Ginsenoside-Rg2	Rha^1-^{2}Glc-	H
Ginsenoside-Rf	Glc^1-^{2}Glc-	H
Notoginsenoside-R1	Xyl^1-^{2}Glc-	Glc-

PPD-type:

Name	R_1	R_2
Protopanaxadiol	H	H
Ginsenoside-Rb1	Glc^1-^{2}Glc-	Glc^1-^{6}Glc-
Ginsenoside-Rb2	Glc^1-^{2}Glc-	$Ara(p)^1$-^{6}Glc-
Ginsenoside-Rb3	Glc^1-^{2}Glc-	Xyl^1-^{6}Glc
Ginsenoside-Rh2	Glc-	H
Ginsenoside-Rg3	Glc-^{2}Glc	H

Fig. 1. Structures of saponins present in this review.

antiviral effect. Rb1 exhibited more significant antiviral activity than Rh2, possibly because Rh2 has only one carbohydrate moiety at position R1, whereas Rb1 has two separate carbohydrate chains (Fig. 1) [23].

P. notoginseng root water extract (PNR) has been shown to prevent H1N1-induced mortality and weight loss in BALB/c mice by increasing the natural killer (NK) cell activity of splenocytes and activating the type-I interferon (IFN-1) mediated immune response in macrophages. PNR-induced IRF3 phosphorylation through TANK-binding kinase 1 (TBK1) triggers the release of IFN-1, which interacts with a component of the JAK/STAT pathway to activate the phosphorylation of STAT1 and stimulation of the IFN-stimulated genes. As a result, the viral protein and viral mRNA expression were decreased by pretreatment of A/PR8/34-infected RAW 264.7 cells with PNR (Fig. 2) [24]. Similarly, a water extract of *P. ginseng* mixed with other herbal medicines (OCD20015-V009) also improves the survival of BALB/c mice exposed to H1N1. OCD20015-V009 induced the antiviral potential of RAW 264.7 cells by phosphorylating the type-I IFN-related proteins (STAT1 and TBK-1) and triggering the production of proinflammatory cytokines (TNF-α and IL-6) (Fig. 2) [25]. It has been reported that compared to non-fermented ginseng extracts, fermented red ginseng extracts containing various active components, such as PPT, PPD, Rh2, and Compound K, showed more potent antiviral activity against various influenza virus strains H5N1, H3N2, H1N1, and H7N9. Moreover, fermented ginseng protected against A/WSN/1933 (H1N1) virus in both wild-types (C57BL/6 and BALB/c mice) and mutant mice (CD4 T cell-deficient, CD8 T cell-deficient, B cell-deficient and MHCII deficient). In addition, fermented red ginseng extracts exhibited modest viral neutralizing efficacy by suppressing hemagglutination and neuraminidase activity. It is hypothesized that the combined effects of multiple substances in fermented ginseng samples may have such antiviral effects against influenza strains of various subtypes. Mice that survived the initial infection or were shielded from it would establish robust immunity against the secondary infection with homologous and dissimilar strains [26]. The effects of ginseng extract on protective immunity from lethal infections against highly pathogenic (HP) H5N1 were also proven in mice and ferrets [27]. During the early stage of infection, black ginseng (BG) significantly increased the granulocyte-macrophage colony-stimulating factor (GM-CSF) which is required for immune homeostasis in the lung. BG stimulated the production of T cell growth factors IL-2 and IFN-γ, which boosted immune function, limited viral replication, and euthanized virus-infected host cells upon viral infection. During the recovery phase of infection, the production of IL-10 stimulated by BG relieved the excessive inflammatory responses and minimized potential host tissue injury. Due to its ability to enhance immune responses, black ginseng may be developed as an oral alternative antiviral adjunctive therapy for the prevention of influenza A virus infections [28]. A report showed that ginseng extract and vitamin C synergistically activate immune cells such as T and NK cells, suppressed H1N1 virus replication, and increased the survival rate of vitamin C-depleted Gulo (−/−) mice. In the HE-stained lungs, the administration of red ginseng and vitamin C reduced the lung inflammation with the induction of TNF-a and IFN-γ (Fig. 3) [29]. The environmentally friendly synthesis of quasi-silver nanoparticles (AgNPs) with an aqueous ginseng extract was developed as a biomaterial applications, and it was also found to be virucidal against the influenza A virus (strain A/PR/8) [30]. In terms of over-the-counter preparations, two randomized, double-blind, and placebo-controlled trials were conducted to determine that orally administrating *P. quinquefolius* water extract (CVT-E002) twice daily could prevent acute respiratory illness caused by the influenza A virus [31].

4. Human immunodeficiency virus type 1 (HIV-1)

For HIV-1, the invention of highly active antiretroviral drug therapy (HAART) has proven beneficial in 80-90% of HIV/AIDS patients; however, long-term HAART causes many adverse effects and ultimately results in virological treatment failure with a high frequency of resistance mutations in HIV-1-infected patients [32,33]. Recent research found that long-term Korean Red Ginseng (KRG) consumption improved HIV-1 patient survival prior to HAART by slowing the decline in CD4+ T cell count [34–36] and postponing the appearance of resistance mutations in HIV-1 patients [37].

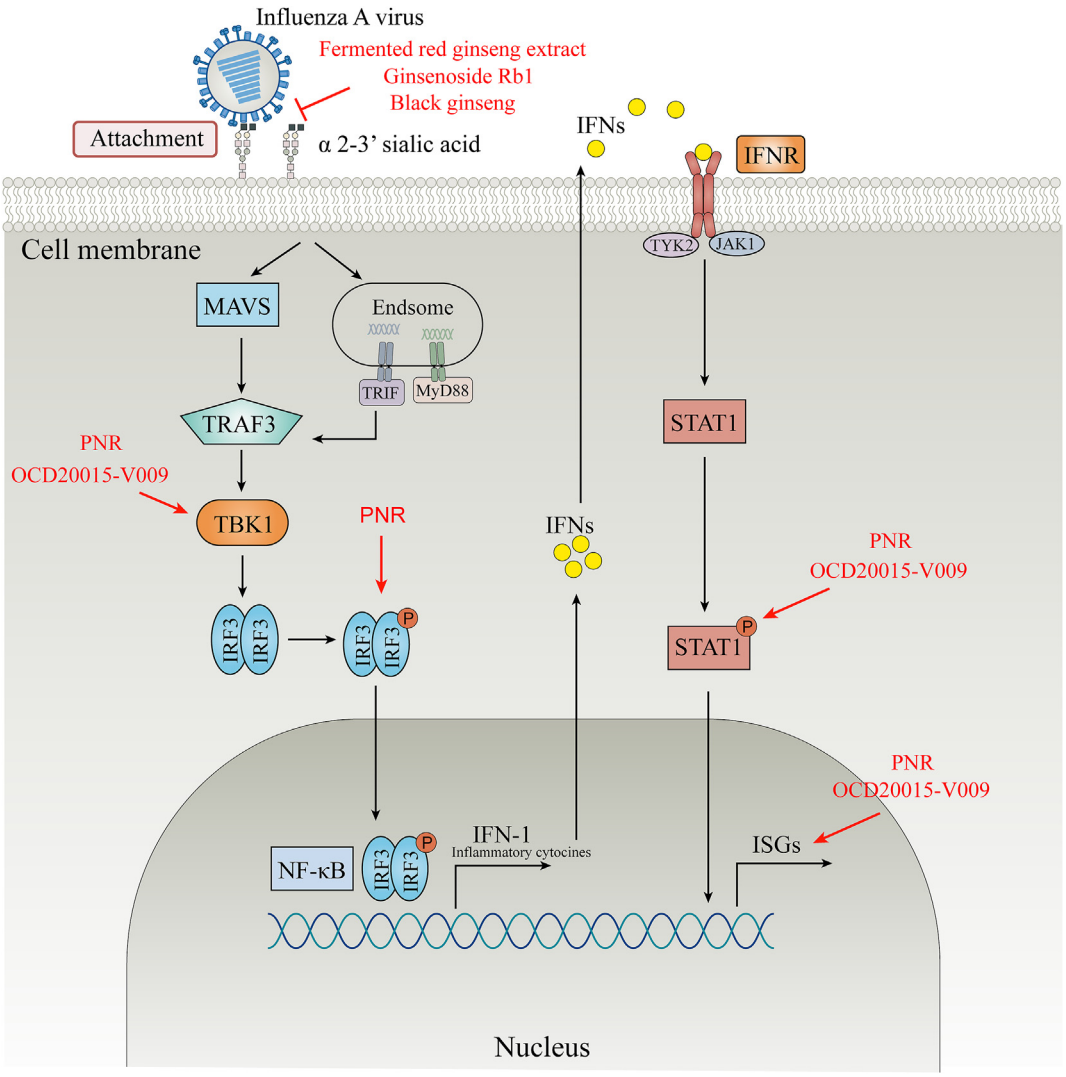


Fig. 2. A schematic of the antiviral mechanism against influenza A virus infection *in vitro*. ('↑' represents activation, stimulation or upregulation, whereas 'T' represents inhibition, decrease or downregulation).

Concurrent therapy with KRG and HAART has been presumed to be a potential regimen for treating HIV-1 disease [38].

5. Enterovirus (EV)

Coxsackieviruses numbered enteroviruses, rhinoviruses, echoviruses and poliovirus are members of the genus *Enterovirus* (EV) of the family *Picornaviridae* [39], of which the first three were included in this review.

5.1. Coxsackievirus

Coxsackievirus, especially Group B Coxsackieviruses (CVBs), are known to be associated with subacute, acute, and chronic virus-induced myocarditis [40]. *P. notoginseng* saponins (PNS) treatment reduced serum levels of IL-6 and TNF-α, which alleviated myocardial injuries in CVB3-induced myocarditis. In addition, PNS inhibited CVB3 replication by activating the CSE/H_2S pathway during the early stage of the disease and protected the cardiac cells from H_2O_2-mediated apoptosis [41]. In addition, the administration of 20(S)-protopanaxtriol reduced mononuclear cell infiltration, relieved myocardium damage, and decreased the plasma levels of creatine kinase (CK) and lactase dehydrogenase (LDH) in CVB-induced mice, which suggests 20(S)-protopanaxtriol as a possible therapeutic option for viral myocarditis [42].

5.2. Enterovirus

Hand, foot, and mouth disease (HFMD) is widespread in infants and children, and it has typical clinical features of fever, a loss of appetite, and a blistering skin rash [43]. As the causative pathogen of HFMD, the enterovirus A species human enterovirus 71 (EV71) can induce apoptosis and autophagy in neural cells, which is associated with fatal neurological complications [44]. Kang et al demonstrated that Rb1 exhibited complete protection from EV71-induced paralysis and protection. Rb1 restricted EV71 replication mainly through inducing cell-mediated immune responses such as TNF-α, IFN-γ, and IL-10, as well as humoral immune responses such as IgA and IgGs. Meanwhile, Rb1 acted as an immune stimulant in EV71-infected cells by potentiating IFN-β production and IFN-β

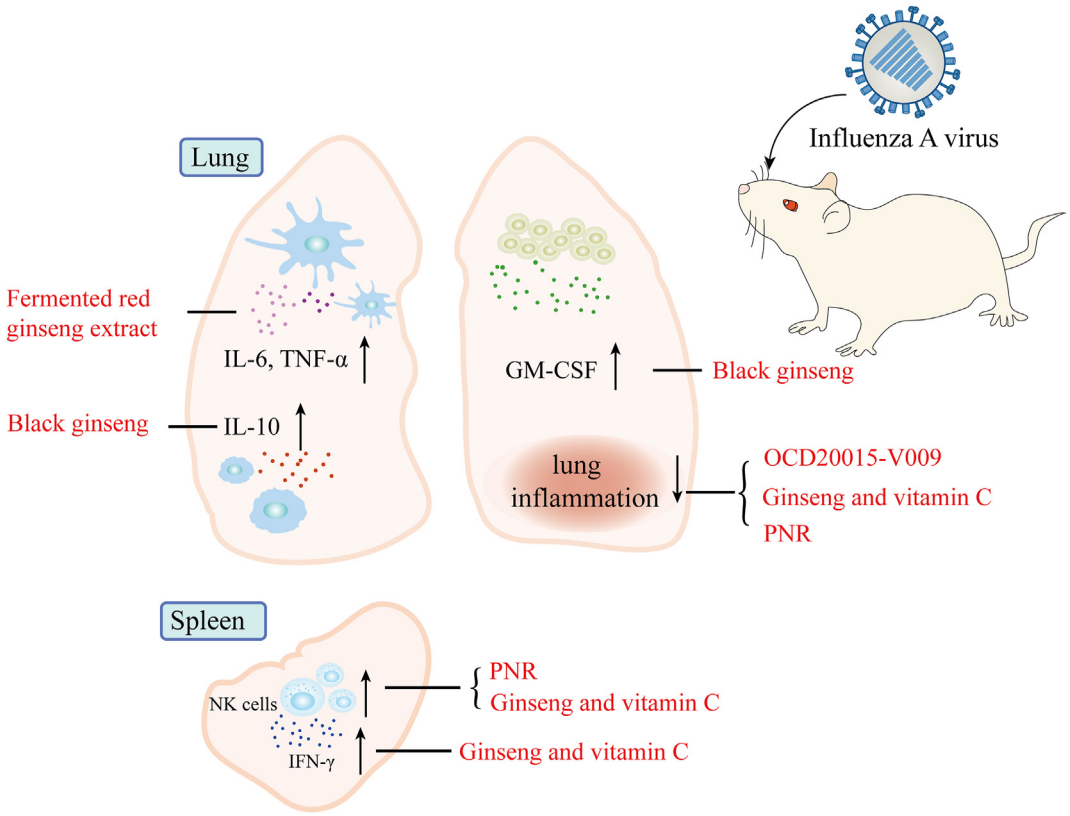


Fig. 3. *In vivo* efficacy of antiviral protection against influenza A virus infection.

downstream effectors MxA [45]. However, the PPT-type ginsenosides Re, Rf, and Rg2 exhibited no significant antiviral activity in the treatment of EV71 infection, implying that the antiviral effect of ginsenosides against EV71 is structure-dependent [46].

5.3. Rhinovirus

Rhinovirus infection can lead to bronchiolitis, early wheezing illness, and even severe exacerbation of asthma [47]. Despite being discovered over 50 years ago, rhinovirus has no approved antiviral medication or vaccine [48]. The PPT-type ginsenosides Rf and Rg2 are significantly effective in the treatment of human rhinovirus 3 (HRV3) infection, with lower toxicity than the commonly used antiviral drug ribavirin [46].

6. Hemagglutinating virus of Japan (HVJ)

HVJ, which is known to cause pneumonia, is one of the most prevalent and important naturally occurring infections of mice [49]. Among dammarane-type ginsenosides (Rb1, -Rb2, -Rd, -Re, and -Rg2) and oleanolic acid-type ginsenoside (Ro, Rb2), oral administration of Rb2 provided the most effective protection against fatal HVJ infection in mice by inhibiting viral growth in the lungs and enhancing mucosal immunity. In a comparison of the growth inhibition effect against HVJ infection, only 20(S)-ginsenoside-Rg3 elicited partial protection, rather than 20(R)-ginsenoside-Rg3 [50].

7. Rotavirus (RV)

Rotavirus is an envelope-free virus of the family *Reoviridae* in the subfamily *Sedoreovirinae* and belongs to the genus Rotavirus [51]. RVs are a major cause of viral gastroenteritis in human infants and children under 5 years of age [52]. Consecutive oral administration of the ginsenoside Rb2 showed a significant reduction in RV-induced diarrhea and virus growth in the bowels, which exerted a better antiviral effect than its hydrolytic product 20(S)-ginsenoside Rg3 with the higher suppression of the total diarrhea

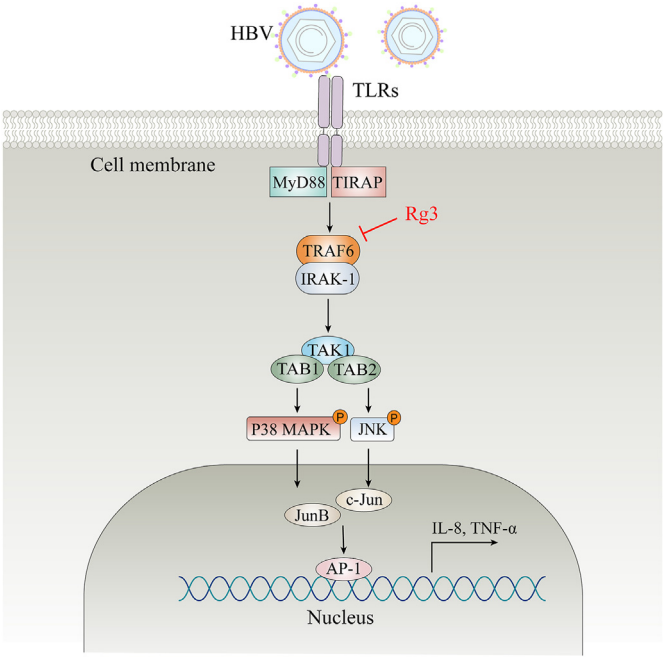


Fig. 4. A schematic of the antiviral mechanism of Rg3 against HBV *in vitro*.

score than with ginsenoside Rb2. The antiviral activity of 20(S)-ginsenoside Rg3 was associated with the activation of mucosal immune systems [53]. However, 20(R)-ginsenoside Rg3, an epimeric type of 20(S)-ginsenoside Rg3, was inactive.

8. Herpesvirus

The herpesviruses have been classified into three subfamilies *Alphaherpesvirinae*, *Betaherpesvirinae,* and *Gammaherpesvirinae,* and infected a large proportion of the human population. It is composed of a lipid envelope, tegument, an icosahedral nucleocapsid, and a core containing double-stranded DNA [54,55].

8.1. Murine gammaherpesvirus 68 (MHV-68)

MHV-68 has been used as an experimental model for human gammaherpesvirus pathogenesis, such as the Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) [56,57]. EBV and KSHV are characterized by their ability to establish a lifelong latent infection in lymphocytes as well as induce lymphoproliferative diseases. Both are oncoviruses [58]. 20(R)-Ginsenoside Rh2 was found to impede the replication and proliferation of MHV-68 by suppressing the expression of the lytic gene KSHV K8α, which is required for viral replication. In addition, 20(R)-ginsenoside Rh2 blocked the reactivation of KSHV by suppressing the mRNA level of KSHV replication and transcription activator and viral DNA amplification [59,60]. Furthermore, the ginsenoside isomers 20(R)- and 20(S)-Rg3 have been reported to possess significant antiviral efficacies against human gammaherpesvirus and murine model virus MHV-68 through suppressing the p38 and JNK signaling pathways, but 20(S)-ginsenoside Rg3 was more effective than 20(R)-ginsenoside [61].

8.2. Herpes simplex virus (HSV)

HSV belongs to the *Alphaherpesvirinae* subfamily. Herpes simplex virus type 1 (HSV-1) causes gingivitis and other oral infections and is extremely common in the human population [62]. Infection with type 2 (HSV-2) leads to genital ulcer disease and neonatal herpes and results in global sexual and reproductive health emergencies [63]. No vaccines against HSV are available [64], and common treatment with nucleoside analog drugs, such as acyclovir, is associated with drug resistance [65]. The prevalence of acyclovir-resistant HSV accounted for 17% of HSV-1-infected patients, and alternative antiviral options remain an unmet need in this clinical setting [66]. Previous studies have shown that the administration of KRG regulated vaginal and systemic HSV infectivity. Additionally, local lymph nodes and the infected tissues showed elevation of the granzyme B and FasL pathways, further enhancing NK cell activity [67]. Recent studies have shown that ginsenoside 20(S)-Rg3 has an antiviral effect against both HSV-1 and HSV-2 and the potential to prevent increased drug resistance when used together with valacyclovir. The possible mechanism for the protective effects of 20(S)-Rg3 may involve the prevention of virus-host interaction by binding with a viral attachment protein or an epidermal growth factor receptor [60]. Thus, it is desirable to develop new anti-HSV agents that can replace or complement acyclovir.

9. Hepatitis B virus (HBV)

Chronic HBV infection has caused progressive liver damage, life-threatening cirrhosis, and hepatocellular carcinoma [68]. Although current therapies can maintain viral suppression and reduce the risk of liver-related complications, lifetime treatment is associated with limited efficacy, high costs, drug resistance, and numerous potential side effects [69]. Patients with chronic hepatitis B (CHB) were administered antiviral agents and KRG powder capsules resulted in the downregulation of the non-invasive fibrosis serologic markers (type IV collagen, hyaluronic acid, and transforming growth factor-β), indicating that ginseng extract has the potential to be a complementary therapy for chronic hepatitis B [70].

Rg3 is thought to have anti-hepatitis B potential in patients with HBV-induced liver disorders by inhibiting HBV surface antigen (HBsAg), HBV envelope antigen (HBeAg), viral particle formation, and viral replication. The anti-hepatitis B action of Rg3 was connected to the suppression of the TLR-myeloid differentiation primary response gene 88 (MyD88)-dependent pathway through the reduction of TNF receptor-associated factor 6 (TRAF6)/ transforming growth factor activated kinase-1 (TAK1) signaling. In addition, Rg3 blocked JNK and p38 mitogen-activated protein kinases (MAPK) phosphorylation that influence AP-1 activity with the downregulation of c-Jun/JunB complex, and reduced the level of inflammatory cytokines (IL-8 and TNF-α). It could be concluded that Rg3 exhibited HBV proliferation by modulating the JNK/AP-1 pathway (Fig. 4) [71]. Since then, no relevant studies have reported the antiviral effect of Rg3 on HBV.

10. Hepatitis C virus (HCV)

HCV is the leading cause of end-stage liver disease [72]. Direct-acting antiviral (DAA) therapies, including sofosbuvir, have revolutionized HCV treatment and have proven efficacy [73]. Unfortunately, abnormal mitochondrial dynamics caused by HCV and DAA may contribute to persistent HCV infection [74,75]. Ginsenoside Rg3 displayed anti-HCV activity with a reduction in HCV RNA and the HCV core protein. Rg3 inhibited HCV propagation effectively through restoring HCV-induced degradation of cytoplasmic p21 and abnormal mitochondrial fission via the downregulation of dynamin-related protein 1. Rg3 treatment rescued the abnormal mitophagy caused by HCV infection or DAA treatment. These results imply that ginsenoside Rg3 may interact with sofosbuvir in a complementary and synergistic manner [76].

11. Grass carp reovirus (GCRV)

GCRV, a dsRNA virus, belongs to Group C of the *Aquareoviruses* and is a pathogen causing a high mortality rate among grass carp, seriously affecting the grass carp cultivation industry [2,77]. Ginsenoside Rg3 appears to be effective against GCRV infection in grass carp ovarian epithelial cells (CO) in the early stage. Rg3 treatment boost host immune activity by triggering immune-related genes in the IFN-I pathway (IRF7, IRF3, Myd88, and IFN-I) and decreasing the expression of pro-inflammatory cytokines TNF-α. In addition, ginsenoside Rg3 cells exhibited higher antioxidant responses than GCRV-infected cells, including total antioxidant capacity, superoxide dismutase, catalase, and glutathione contents [78].

12. Newcastle disease virus (NDV)

NDV belongs to the *Paramyxovirus* family [79], which infects various species with varying degrees of susceptibility in addition to domesticated avian species [80]. Ginseng stem-leaf saponins (GSLS), which contains various ginsenosides (Rg1, Re, Rb1, Rb2, Rf, Rc, and Rd) promoted significantly higher antibody responses among chickens immunized with live Newcastle disease (ND) vaccines. It showed that oral administration of GSLS solution before vaccination increased NDV-specific hemagglutination inhibition titer, lymphocyte proliferation, intestinal mucosal IgA + cells, and intestinal intraepithelial lymphocytes, which suggested GSLS as an immune potentiating effect on the NDV vaccine [81,82] .

13. Pestivirus

The genus *Pestivirus* within the *Flaviviridae* family contains bovine viral diarrhea virus (BVDV) and classical swine fever virus (CSFV) [83,84]. BVDV infection has generated considerable economic losses in the cattle industry and has become a severe laboratory contaminant in fetal bovine serum [85]. Infection with CSFV leads to contagious febrile viral swine disease with high morbidity and mortality [86]. Ginsenosides Rb2 and Rb3 were reported to inhibit BVDV and CSFV replication and proliferation in MDBK cells. Rb2 significantly reduced the translation process mediated by the *Pestivirus* internal ribosome entry site (IRES) through luciferase reporter assay, which might be responsible for the antiviral mechanism of Rb2 [87].

14. Respiratory syncytial virus (RSV)

RSV belongs to the family of *Pneumoviridae*, genus *Orthopneumovirus* [88]. RSV leads to severe acute lower respiratory infection (ALRI), resulting in a major cause of hospital admission and significant mortality in children [89].

The underlying mechanisms by which *P. ginseng* extract provides protective efficacy against RSV *in vivo* and *in vitro* are through the inhibition of viral replication and cell death, the blockage of the induction of proinflammatory cytokines and immune cells migrating into the lung, the enhancement of antiviral IFN-γ production, the reduction of weight loss and lung disease in mice [90–92]. Based on the results, the consumption of *P. ginseng* extract in healthy individuals is of great benefit due to the prevention and alleviation of unexpected RSV infections.

A placebo-controlled clinical trial showed that *P. quinquefolius* (CVT-E002) was effective in preventing acute respiratory illness (ARI) symptoms due to RSV [31], with no serious adverse events reported in phase II clinical trial [93], which indicated that *P. quinquefolius* was well tolerated and merits additional evaluation for treating ARI.

15. Coronavirus

Coronaviruses, resulting in severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19), tend to mutate and recombine easily due to the low fidelity of RNA replication, which results in increasing the evolution and diversity of the virus in the wild [94,95]. *Panax* ginseng was shown to be effective against SARS in the 2002/2003 epidemic and also COVID-19 [96]. PEGylated nanoparticle albumin-bound (PNAB) was reported to suppress H4-mediated NET, NF-κB and SREBP2-mediated cytokine storms in SARS-CoV-2 ICU patients. Furthermore, these nanotherapeutics could alleviate blood clot formation and vascular inflammation [97]. This finding supports the promising capability of PNAB-steroidal ginsenoside nanotherapeutics as potential tools for treating patients with severe COVID-19.

16. Conclusion and future prospects

The widespread epidemic of viral infections has become a serious public health problem. Synthetic drugs have shown remarkable success in alleviating viral infections; however, the serious side effects cannot be ignored. Long-term therapy with antiviral nucleoside analogs or hormones results in severe anemia, potential liver damage, and drug resistance. The present review summarizes that 12 bioactive saponins and extracts from three kinds of *Panax* species exhibit various antiviral efficacies through multiple mechanisms, such as directly inhibiting viral adsorption and replication and improving host immunity by activating the immune response.

As a result of the differences in processing conditions and *Panax* species, variations in saponin constituents may result in the generation of distinct antiviral activities [10,98]. RG is prepared by steaming fresh ginseng before drying it, whereas black ginseng (BG) is made by repeating the same procedure nine times. The 7-fold higher levels of acid polysaccharides in BG than RG may be possible to explained why BG exhibited greater effectiveness against the influenza virus [28]. The anti-influenza properties of ginseng fermentation have been reported to be enhanced by the conversion of the main ginsenosides (Rb1, Rb2, Rc) into their metabolites by cleaving the sugar moieties at C-3, C-6, or C-20 has been reported to improve the effects of [10,26]. As a result, further research into the conversion of active ingredients caused by different processing methods is warranted, providing a more reliable scientific basis for ginseng processing.

Among all saponins, Rg3 offers the broadest spectrum of antiviral efficacy against HVJ, RV, HSV, HBV, HCV, and GCRV infections. Notably, Rg3 possesses two epimers from which 20(S)-ginseng saponins can be formed naturally, whereas 20(R)-ginseng saponins can only be obtained through enzyme conversion and microbial transformation from their corresponding 20(S)-isomers [10,61,99]. The isomers exhibit different stereospecificities in their pharmacological effects owing to the different spatial orientation of the hydroxyl group on the chiral center at carbon-20 [61]. For their distinctive chemical structures, 20(S)-Rg3 exerts more effective antiviral activity against human gammaherpesviruses, as well as MHV-68 [61]. The majority of the antiviral research also showed that 20(S)-Rg3 proved to be more effective against HSV, RV, and HJV than 20(R)-Rg3 [50,53,60]. However, there is still controversy on which configuration provides the better biological effect. According to Wright et al, 20(R)-protopanaxadiol, but not 20(S)-protopanaxadiol, exhibited partial protection against HSV [60]. Wang et al discovered that 20(R)-ginseng saponins exerted more potent bioactivities including antifatigue, antioxidative, and antitumor properties [99]. Future research should focus on the structure-activity relationship of 20(R)-ginseng saponins or 20(S)-ginseng saponins and their underlying mechanisms of antiviral action, as well as clinical trials to assess their efficacy against various viral infections.

Moreover, KRG or Rg3 combined with other antiviral drugs, such as HAART and valacyclovir, have shown more positive effects against HIV and HSV infection, respectively, suggesting that *Panax* species plants can be used as adjunctive antiviral therapeutic agents or nutritional supplements to address serious problems such as viral mutation and drug resistance.

Author contributions

Y. Zhang: Writing-original draft. X. Zhong: Writing-review & editing. Z. Xi: Writing-review & editing. Y. Li: Writing-review & editing. H. Xu: Conceptualization, Funding acquisition, Project administration, Supervision, Writing-review & editing. All authors agree to be accountable for all aspects of the work, ensuring integrity and accuracy.

Declaration of competing interest

The authors declare no conflict of interest.

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References

[1] Pecora F, Persico F, Argentiero A, Neglia C, Esposito S. The role of micronutrients in support of the immune response against viral infections. Nutrients 2020;12(10).

[2] Zhang C, Lu LF, Li ZC, Zhou XY, Zhou Y, Chen DD, Li S, Zhang YA. Grass carp reovirus VP56 represses interferon production by degrading phosphorylated IRF7. Fish Shellfish Immunol 2020;99:99–106.

[3] Lundstrom K. Self-amplifying RNA viruses as RNA vaccines. Int J Mol Sci 2020;21(14).

[4] Lampejo T. Influenza and antiviral resistance: an overview. Eur J Clin Microbiol Infect Dis 2020;39(7):1201–8.

[5] Park SE, Na CS, Yoo SA, Seo SH, Son HS. Biotransformation of major ginsenosides in ginsenoside model culture by lactic acid bacteria. J Ginseng Res 2017;41(1):36–42.

[6] Mohanan P, Subramaniyam S, Mathiyalagan R, Yang DC. Molecular signaling of ginsenosides Rb1, Rg1, and Rg3 and their mode of actions. J Ginseng Res 2018;42(2):123–32.

[7] Bai L, Gao J, Wei F, Zhao J, Wang D, Wei J. Therapeutic potential of ginsenosides as an adjuvant treatment for diabetes. Front Pharmacol 2018;9:423.

[8] Liu H, Lu X, Hu Y, Fan X. Chemical constituents of Panax ginseng and Panax notoginseng explain why they differ in therapeutic efficacy. Pharmacol Res 2020;161:105263.

[9] Szczuka D, Nowak A, Zaklos-Szyda M, Kochan E, Szymanska G, Motyl I, Blasiak J. American ginseng (Panax quinquefolium L.) as a source of bioactive phytochemicals with pro-health properties. Nutrients 2019;11(5).

[10] Piao XM, Huo Y, Kang JP, Mathiyalagan R, Zhang H, Yang DU, Kim M, Yang DC, Kang SC, Wang YP. Diversity of ginsenoside profiles produced by various processing technologies. Molecules 2020;25(19).

[11] Nguyen NH, Nguyen CT. Pharmacological effects of ginseng on infectious diseases. Inflammopharmacology 2019;27(5):871–83.

[12] Zhang T, Zhong S, Hou L, Wang Y, Xing X, Guan T, Zhang J, Li T. Computational and experimental characterization of estrogenic activities of 20(S, R)-protopanaxadiol and 20(S, R)-protopanaxatriol. J Ginseng Res 2020;44(5):690–6.

[13] Shin BK, Kwon SW, Park JH. Chemical diversity of ginseng saponins from Panax ginseng. J Ginseng Res 2015;39(4):287–98.

[14] Wensvoort G, Terpstra C, Pol JM, ter Laak EA, Bloemraad M, de Kluyver EP, Kragten C, van Buiten L, den Besten A, Wagenaar F, et al. Mystery swine disease in The Netherlands: the isolation of Lelystad virus. Vet Q 1991;13(3):121–30.

[15] Du T, Nan Y, Xiao S, Zhao Q, Zhou EM. Antiviral strategies against PRRSV infection. Trends Microbiol 2017;25(12):968–79.

[16] Kappes MA, Faaberg KS. PRRSV structure, replication and recombination: origin of phenotype and genotype diversity. Virology 2015;479–480:475–86.

[17] Lunney JK, Fang Y, Ladinig A, Chen N, Li Y, Rowland B, Renukaradhya GJ. Porcine reproductive and respiratory syndrome virus (PRRSV): pathogenesis and interaction with the immune system. Annu Rev Anim Biosci 2016;4:129–54.

[18] Yu ZQ, Yi HY, Ma J, Wei YF, Cai MK, Li Q, Qin CX, Chen YJ, Han XL, Zhong RT, et al. Ginsenoside Rg1 suppresses type 2 PRRSV infection via NF-kappaB signaling pathway in vitro, and provides partial protection against HP-PRRSV in piglet. Viruses 2019;11(11).

[19] Hu Y, Zhang B, Wang W, Zhou J, Li B, He K. Therapeutic effects of saponin components on porcine reproductive and respiratory syndrome virus-infected piglets. J Anim Physiol Anim Nutr (Berl). 2020;104(2):637–44.

[20] Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev 1992;56(1):152–79.

[21] Takashita E, Ichikawa M, Morita H, Ogawa R, Fujisaki S, Shirakura M, Miura H, Nakamura K, Kishida N, Kuwahara T, et al. Human-to-Human transmission of influenza A(H3N2) virus with reduced susceptibility to baloxavir, Japan, february 2019. Emerg Infect Dis 2019;25(11):2108–11.

[22] Joseph U, Su YC, Vijaykrishna D, Smith GJ. The ecology and adaptive evolution of influenza A interspecies transmission. Influenza Other Respir Viruses 2017;11(1):74–84.

[23] Dong W, Farooqui A, Leon AJ, Kelvin DJ. Inhibition of influenza A virus infection by ginsenosides. PLoS One 2017;12(2):e0171936.

[24] Choi JG, Jin YH, Lee H, Oh TW, Yim NH, Cho WK, Ma JY. Protective effect of Panax notoginseng root water extract against influenza A virus infection by enhancing antiviral interferon-mediated immune responses and natural killer cell activity. Front Immunol 2017;8:1542.

[25] Kwon EB, Oh YC, Hwang YH, Li W, Park SM, Kong R, Kim YS, Choi JG. A herbal mixture formula of OCD20015-V009 prophylactic administration to enhance interferon-mediated antiviral activity against influenza A virus. Front Pharmacol 2021;12:764297.

[26] Wang Y, Jung YJ, Kim KH, Kwon Y, Kim YJ, Zhang Z, Kang HS, Wang BZ, Quan FS, Kang SM. Antiviral activity of fermented ginseng extracts against a broad range of influenza viruses. Viruses 2018;10(9).

[27] Park EH, Yum J, Ku KB, Kim HM, Kang YM, Kim JC, Kim JA, Kang YK, Seo SH. Red Ginseng-containing diet helps to protect mice and ferrets from the lethal infection by highly pathogenic H5N1 influenza virus. J Ginseng Res 2014;38(1):40–6.

[28] Kim EH, Kim SW, Park SJ, Kim S, Yu KM, Kim SG, Lee SH, Seo YK, Cho NH, Kang K, et al. Greater efficacy of black ginseng (cj EnerG) over red ginseng against lethal influenza A virus infection. Nutrients 2019;11(8).

[29] Kim H, Jang M, Kim Y, Choi J, Jeon J, Kim J, Hwang YI, Kang JS, Lee WJ. Red ginseng and vitamin C increase immune cell activity and decrease lung inflammation induced by influenza A virus/H1N1 infection. J Pharm Pharmacol 2016;68(3):406–20.

[30] Sreekanth TVM, Nagajyothi PC, Muthuraman P, Enkhtaivan G, Vattikuti SVP, Tettey CO, Kim DH, Shim J, Yoo K. Ultra-sonication-assisted silver nanoparticles using Panax ginseng root extract and their anti-cancer and antiviral activities. J Photochem Photobiol B 2018;188:6–11.

[31] McElhaney JE, Gravenstein S, Cole SK, Davidson E, O'Neill D, Petitjean S, Rumble B, Shan JJ. A placebo-controlled trial of a proprietary extract of North American ginseng (CVT-E002) to prevent acute respiratory illness in institutionalized older adults. J Am Geriatr Soc 2004;52(1):13–9.

[32] Sung H, Jung YS, Kang MW, Bae IG, Chang HH, Woo JH, Cho YK. High frequency of drug resistance mutations in human immunodeficiency virus type 1-infected Korean patients treated with HAART. AIDS Res Hum Retroviruses 2007;23(10):1223–9.

[33] Lu DY, Wu HY, Yarla NS, Xu B, Ding J, Lu TR. HAART in HIV/AIDS treatments: future trends. Infect Disord Drug Targets 2018;18(1):15–22.

[34] Cho YK, Kim JE. Effect of Korean Red Ginseng intake on the survival duration of human immunodeficiency virus type 1 patients. J Ginseng Res 2017;41(2):222–6.

[35] Sung H, Kang SM, Lee MS, Kim TG, Cho YK. Korean red ginseng slows depletion of CD4 T cells in human immunodeficiency virus type 1-infected patients. Clin Diagn Lab Immunol 2005;12(4):497–501.

[36] Sung H, Jung YS, Cho YK. Beneficial effects of a combination of Korean red ginseng and highly active antiretroviral therapy in human immunodeficiency virus type 1-infected patients. Clin Vaccine Immunol 2009;16(8):1127–31.

[37] Cho YK, Kim JE. The frequency of defective genes in vif and vpr genes in 20 hemophiliacs is associated with Korean Red Ginseng and highly active antiretroviral therapy: the impact of lethal mutations in vif and vpr genes on HIV-1 evolution. J Ginseng Res 2021;45(1):149–55.

[38] Cho YK, Kim JE, Woo JH. Korean Red Ginseng increases defective pol gene in peripheral blood mononuclear cells of HIV-1-infected patients; inhibition of its detection during ginseng-based combination therapy. J Ginseng Res 2019;43(4):684–91.

[39] Baggen J, Thibaut HJ, Strating J, van Kuppeveld FJM. The life cycle of non-polio enteroviruses and how to target it. Nat Rev Microbiol 2018;16(6):368–81.

[40] Khanna M, Gautam A, Rajput R, Sharma L. Natural products as a paradigm for the treatment of coxsackievirus - induced myocarditis. Curr Top Med Chem 2020;20(8):607–16.

[41] Pan L, Zhang Y, Lu J, Geng Z, Jia L, Rong X, Wang Z, Zhao Q, Wu R, Chu M, et al. Panax notoginseng saponins ameliorates coxsackievirus B3-induced myocarditis by activating the cystathionine-gamma-lyase/hydrogen sulfide pathway. J Cardiovasc Transl Res 2015;8(9):536–44.

[42] Wang X, Wang Y, Ren Z, Qian C, Li Y, Wang Q, Zhang Y, Zheng L, Jiang J, Yang C, et al. Protective effects of 20(s)-protopanaxtriol on viral myocarditis infected by coxsackievirus B3. Pathobiology 2012;79(6):285–9.

[43] Ventarola D, Bordone L, Silverberg N. Update on hand-foot-and-mouth disease. Clin Dermatol 2015;33(3):340–6.

[44] You L, Chen J, Liu W, Xiang Q, Luo Z, Wang W, Xu W, Wu K, Zhang Q, Liu Y, et al. Enterovirus 71 induces neural cell apoptosis and autophagy through promoting ACOX1 downregulation and ROS generation. Virulence 2020;11(1):537–53.

[45] Kang N, Gao H, He L, Liu Y, Fan H, Xu Q, Yang S. Ginsenoside Rb1 is an immune-stimulatory agent with antiviral activity against enterovirus 71. J Ethnopharmacol 2021;266:113401.

[46] Song JH, Choi HJ, Song HH, Hong EH, Lee BR, Oh SR, Choi K, Yeo SG, Lee YP, Cho S, et al. Antiviral activity of ginsenosides against coxsackievirus B3, enterovirus 71, and human rhinovirus 3. J Ginseng Res 2014;38(3):173–9.

[47] Bergroth E, Aakula M, Elenius V, Remes S, Piippo-Savolainen E, Korppi M, Piedra PA, Bochkov YA, Gern JE, Camargo Jr CA, et al. Rhinovirus type in severe bronchiolitis and the development of asthma. J Allergy Clin Immunol Pract 2020;8(2):588–595 e4.

[48] Makris S, Johnston S. Recent advances in understanding rhinovirus immunity. F1000Res 2018;7.

[49] Fukushima A, Yoo YC, Yoshimatsu K, Matsuzawa K, Tamura M, Tono-oka S, Taniguchi K, Urasawa S, Arikawa J, Azuma I. Effect of MDP-Lys(L18) as a mucosal immunoadjuvant on protection of mucosal infections by Sendai virus and rotavirus. Vaccine 1996;14(6):485–91.

[50] Yoo YC, Lee J, Park SR, Nam KY, Cho YH, Choi JE. Protective effect of ginsenoside-Rb2 from Korean red ginseng on the lethal infection of haemagglutinating virus of Japan in mice. J Ginseng Res 2013;37(1):80–6.

[51] Sadiq A, Bostan N, Yinda KC, Naseem S, Sattar S. Rotavirus: genetics, pathogenesis and vaccine advances. Rev Med Virol 2018;28(6):e2003.

[52] Mortality GBD. Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459–544. 10053.

[53] Yang H, Oh KH, Kim HJ, Cho YH, Yoo YC. Ginsenoside-Rb2 and 20(S)-Ginsenoside-Rg3 from Korean red ginseng prevent rotavirus infection in newborn mice. J Microbiol Biotechnol 2018;28(3):391–6.
[54] Connolly SA, Jardetzky TS, Longnecker R. The structural basis of herpesvirus entry. Nat Rev Microbiol 2021;19(2):110–21.
[55] Dadwal SS. Herpes virus infections other than cytomegalovirus in the recipients of hematopoietic stem cell transplantation. Infect Dis Clin North Am 2019;33(2):467–84.
[56] Simas JP, Efstathiou S. Murine gammaherpesvirus 68: a model for the study of gammaherpesvirus pathogenesis. Trends Microbiol 1998;6(7):276–82.
[57] Aligo J, Walker M, Bugelski P, Weinstock D. Is murine gammaherpesvirus-68 (MHV-68) a suitable immunotoxicological model for examining immunomodulatory drug-associated viral recrudescence? J Immunotoxicol 2015;12(1):1–15.
[58] Manners O, Murphy JC, Coleman A, Hughes DJ, Whitehouse A. Contribution of the KSHV and EBV lytic cycles to tumourigenesis. Curr Opin Virol 2018;32:60–70.
[59] Kang S, Im K, Kim G, Min H. Antiviral activity of 20(R)-ginsenoside Rh2 against murine gammaherpesvirus. J Ginseng Res 2017;41(4):496–502.
[60] Wright S, Altman E. Inhibition of herpes simplex viruses, types 1 and 2, by ginsenoside 20(S)-Rg3. J Microbiol Biotechnol 2020;30(1):101–8.
[61] Kang S, Song MJ, Min H. Antiviral activity of ginsenoside Rg3 isomers against gammaherpesvirus through inhibition of p38- and JNK-associated pathways. Journal of Functional Foods 2018;40:219–28.
[62] Petti S, Lodi G. The controversial natural history of oral herpes simplex virus type 1 infection. Oral Dis 2019;25(8):1850–65.
[63] Schiffer JT, Gottlieb SL. Biologic interactions between HSV-2 and HIV-1 and possible implications for HSV vaccine development. Vaccine 2019;37(50):7363–71.
[64] Xu X, Zhang Y, Li Q. Characteristics of herpes simplex virus infection and pathogenesis suggest a strategy for vaccine development. Rev Med Virol 2019;29(4):e2054.
[65] Daikoku T, Tannai H, Honda M, Onoe T, Matsuo K, Onoye Y, Nishizawa M, Kawana T, Okuda T, Hasegawa T, et al. Subclinical generation of acyclovir-resistant herpes simplex virus with mutation of homopolymeric guanosine strings during acyclovir therapy. J Dermatol Sci 2016;82(3):160–5.
[66] Anton-Vazquez V, Mehra V, Mbisa JL, Bradshaw D, Basu TN, Daly ML, Mufti GJ, Pagliuca A, Potter V, Zuckerman M. Challenges of aciclovir-resistant HSV infection in allogeneic bone marrow transplant recipients. J Clin Virol 2020;128:104421.
[67] Cho A, Roh YS, Uyangaa E, Park S, Kim JW, Lim KH, Kwon J, Eo SK, Lim CW, Kim B. Protective effects of red ginseng extract against vaginal herpes simplex virus infection. J Ginseng Res 2013;37(2):210–8.
[68] Heim K, Neumann-Haefelin C, Thimme R, Hofmann M. Heterogeneity of HBV-specific CD8(+) T-cell failure: implications for immunotherapy. Front Immunol 2019;10:2240.
[69] Gane EJ. Future anti-HBV strategies. Liver Int 2017;37(Suppl 1):40–4.
[70] Choi SH, Yang KJ, Lee DS. Effects of complementary combination therapy of Korean red ginseng and antiviral agents in chronic hepatitis B. J Altern Complement Med 2016;22(12):964–9.
[71] Kang LJ, Choi YJ, Lee SG. Stimulation of TRAF6/TAK1 degradation and inhibition of JNK/AP-1 signalling by ginsenoside Rg3 attenuates hepatitis B virus replication. Int J Biochem Cell Biol 2013;45(11):2612–21.
[72] Westerhoff M, Ahn J. Chronic hepatitis C and direct acting antivirals. Surg Pathol Clin 2018;11(2):287–96.
[73] Baumert TF, Berg T, Lim JK, Nelson DR. Status of direct-acting antiviral therapy for hepatitis C virus infection and remaining challenges. Gastroenterology 2019;156(2):431–45.
[74] Kim SJ, Syed GH, Khan M, Chiu WW, Sohail MA, Gish RG, Siddiqui A. Hepatitis C virus triggers mitochondrial fission and attenuates apoptosis to promote viral persistence. Proc Natl Acad Sci U S A 2014;111(17):6413–8.
[75] Jassey A, Liu CH, Changou CA, Richardson CD, Hsu HY, Lin LT. Hepatitis C virus non-structural protein 5A (NS5A) disrupts mitochondrial dynamics and induces mitophagy. Cells 2019;8(4).
[76] Kim SJ, Jang JY, Kim EJ, Cho EK, Ahn DG, Kim C, Park HS, Jeong SW, Lee SH, Kim SG, et al. Ginsenoside Rg3 restores hepatitis C virus-induced aberrant mitochondrial dynamics and inhibits virus propagation. Hepatology 2017;66(3):758–71.
[77] Reshi L, Wu JL, Wang HV, Hong JR. Aquatic viruses induce host cell death pathways and its application. Virus Res 2016;211:133–44.
[78] Dai J, Zhang L, Zhang P, Shu H, Mao A, Li Y. Ginsenoside Rg3 inhibits grass carp reovirus replication in grass carp ovarian epithelial cells. Microb Pathog 2020;144:104174.
[79] Cox RM, Plemper RK. Structure and organization of paramyxovirus particles. Curr Opin Virol 2017;24:105–14.
[80] Gowthaman V, Singh SD, Dhama K, Desingu PA, Kumar A, Malik YS, Munir M. Isolation and characterization of genotype XIII Newcastle disease virus from Emu in India. Virusdisease 2016;27(3):315–8.
[81] Ma X, Bi S, Wang Y, Chi X, Hu S. Combined adjuvant effect of ginseng stem-leaf saponins and selenium on immune responses to a live bivalent vaccine of Newcastle disease virus and infectious bronchitis virus in chickens. Poult Sci 2019;98(9):3548–56.
[82] Zhai L, Li Y, Wang W, Wang Y, Hu S. Effect of oral administration of ginseng stem-and-leaf saponins (GSLS) on the immune responses to Newcastle disease vaccine in chickens. Vaccine 2011;29(31):5007–14.
[83] Blome S, Staubach C, Henke J, Carlson J, Beer M. Classical swine fever-an updated review. Viruses 2017;9(4).
[84] Chernick A, Ambagala A, Orsel K, Wasmuth JD, van Marle G, van der Meer F. Bovine viral diarrhea virus genomic variation within persistently infected cattle. Infect Genet Evol 2018;58:218–23.
[85] Pecora A, Perez Aguirreburualde MS, Ridpath JF, Dus Santos MJ. Molecular characterization of pestiviruses in fetal bovine sera originating from Argentina: evidence of circulation of HoBi-like viruses. Front Vet Sci 2019;6:359.
[86] Tong W, Zheng H, Li GX, Gao F, Shan TL, Zhou YJ, Yu H, Jiang YF, Yu LX, Li LW, et al. Recombinant pseudorabies virus expressing E2 of classical swine fever virus (CSFV) protects against both virulent pseudorabies virus and CSFV. Antiviral Res 2020;173:104652.
[87] Tan B, Giangaspero M, Sun N, Jin Y, Liu K, Wang Q, Cheng S, Wang Y, Zhang S. Antiviral effect of ginsenoside Rb2 and Rb3 against bovine viral diarrhea virus and classical swine fever virus in vitro. Front Vet Sci 2021;8:764909.
[88] Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ 2019;366:l5021.
[89] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, Polack FP, Balsells E, Acacio S, Aguayo C, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946–58. 10098.
[90] Lee JS, Ko EJ, Hwang HS, Lee YN, Kwon YM, Kim MC, Kang SM. Antiviral activity of ginseng extract against respiratory syncytial virus infection. Int J Mol Med 2014;34(1):183–90.
[91] Lee JS, Lee YN, Lee YT, Hwang HS, Kim KH, Ko EJ, Kim MC, Kang SM. Ginseng protects against respiratory syncytial virus by modulating multiple immune cells and inhibiting viral replication. Nutrients 2015;7(2):1021–36.
[92] Lee JS, Cho MK, Hwang HS, Ko EJ, Lee YN, Kwon YM, Kim MC, Kim KH, Lee YT, Jung YJ, et al. Ginseng diminishes lung disease in mice immunized with formalin-inactivated respiratory syncytial virus after challenge by modulating host immune responses. J Interferon Cytokine Res 2014;34(11):902–14.
[93] Vohra S, Johnston BC, Laycock KL, Midodzi WK, Dhunnoo I, Harris E, Baydala L. Safety and tolerability of North American ginseng extract in the treatment of pediatric upper respiratory tract infection: a phase II randomized, controlled trial of 2 dosing schedules. Pediatrics 2008;122(2):e402–10.
[94] Xie X, Hu L, Xue H, Xiong Y, Panayi AC, Lin Z, Chen L, Yan C, Zhou W, Mi B, et al. Prognosis and treatment of complications associated with COVID-19: a systematic review and meta-analysis. Acta Materia Medica.1(1):124-137.
[95] Yang J, Yang Y. Regulatory lessons from China's COVID-19 vaccines development and approval policies. Acta Materia Medica.1(1):96-105.
[96] Oesch F, Oesch-Bartlomowicz B, Efferth T. Toxicity as prime selection criterion among SARS-active herbal medications. Phytomedicine 2021;85:153476.
[97] Park HH, Kim H, Lee HS, Seo EU, Kim JE, Lee JH, Mun YH, Yoo SY, An J, Yun MY, et al. PEGylated nanoparticle albumin-bound steroidal ginsenoside derivatives ameliorate SARS-CoV-2-mediated hyper-inflammatory responses. Biomaterials 2021;273:120827.
[98] Sharma P, Tyagi A, Bhansali P, Pareek S, Singh V, Ilyas A, Mishra R, Poddar NK. Saponins: extraction, bio-medicinal properties and way forward to anti-viral representatives. Food Chem Toxicol 2021;150:112075.
[99] Wang C, Liu J, Deng J, Wang J, Weng W, Chu H, Meng Q. Advances in the chemistry, pharmacological diversity, and metabolism of 20(R)-ginseng saponins. J Ginseng Res 2020;44(1):14–23.