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Review Article

Antiviral activities of ginseng and its potential and putative benefits against monkeypox virus: A mini review

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ABSTRACT

Due to the Covid-19 pandemic more than 6 million people have died, and it has bought unprecedented challenges to our lives. The recent outbreak of monkeypox virus (MPXV) has brought out new tensions among the scientific community. Currently, there is no specific treatment protocol for MPXV. Several antivirals, vaccinia immune globulin (VIG) and smallpox vaccines have been used to treat MPXV. Ginseng, one of the more famous among traditional medicines, has been used for infectious disease for thousands of years. It has shown promising antiviral effects. Ginseng could be used as a potential adaptogenic agent to help prevent infection by MPXV along with other drugs and vaccines. In this mini review, we explore the possible use of ginseng in MPXV prevention based on its antiviral activity.

1. Introduction

While people from all over the world still struggle with the COVID-19 pandemic, the new outbreak of monkeypox virus has raised concern among public health authorities. Monkeypox virus is a double-stranded DNA virus of the genus orthopoxviruses, which also includes variola, cowpox (CPX), and vaccinia viruses. MPXV virus was first isolated from monkeys; however, the natural hosts of monkeypox virus also include rope squirrels, tree squirrels, Gambian pouched rats, and dormice. MPXV is a zoonotic virus of the *Orthopoxvirus* genus and Poxviridae family, which includes several other zoonotic viruses like vaccinia virus, cowpox virus, and variola virus. Electron microscopy reveals it as a brick-shaped DNA virus with a lipoprotein envelope and a genome size of ≈200 kb [1,2]. Till now, the whole genomic analysis has identified two genetically distinct clades of MPXV: the Central African clade (CAC) and the West African clade (WAC) [3]. Morbidity, mortality, transmissibility, viral load, and clinical manifestations are more pronounced in Central African MPXV infection [4,5], which can be explained by the genetic differences between these two clades [6,7]. Monkeypox was first detected in 1958 in Denmark among monkeys captured for research studies, thus the name "monkeypox" [8]. However, African rodents were later identified as the natural reservoir of the virus, while monkeys and humans are considered disease hosts [9]. Human monkeypox was first detected in 1970 in the Democratic Republic of Congo (DRC) by a surveillance study nine months after the DRC was declared a smallpox-

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eradicated region by the WHO [10,11]. MPXV has been endemic to Central and West Africa since its discovery, with most cases coming from DRC, but an alarming rise in the last two decades has been observed by surveillance systems [12].

Smallpox eradication and subsequent discontinuation of smallpox vaccination after 1980 resulted in declining herd immunity, a key factor behind the rise of human monkeypox cases in the endemic regions [13,14]. Unvaccinated populations, including younger age groups, are more susceptible to MPXV infection. Other contributing factors are poverty, civil wars, forced migration, and changes in the landscape, climate, and demography disrupting the reservoir species' natural environment. These factors resulted in an expansion of monkeypox-carrying small mammals and increased human contact with such animals across West and Central Africa [11,15].

Interestingly, researchers supported terminating routine smallpox vaccination in monkeypox endemic areas as the virus is considered less transmissible and is incapable of persisting in the human population [16]. Yet, we have seen sporadic cases and clusters from non-endemic regions in the later years. The United States reported 53 human cases in 2003, and Gambian giant rats imported from Ghana were identified as the source of infection. From 2018 to 2021, human monkeypox cases were reported in Israel, Singapore, the United Kingdom, and the United States, and all of these cases were traced back to people with travel histories of Nigeria [17–20]. Since early May 2022, countries outside Africa have reported monkeypox cases. Most cases reported travelling to European and North American countries rather than the endemic areas like West or Central Africa. Since its discovery, this is the most significant number of monkeypox cases and clusters that have occurred concurrently in diverse geographical areas, including inside and outside endemic regions. In this multi-country outbreak of monkeypox, most patients were identified as men who have sex with men [21]. MPXV can infect people through direct contact with an infected animal or person during intimate or prolonged contact, including sexual exposure. Indirect transmission can occur via contaminated fomites, including the personal belongings of a monkeypox patient [11,22]. MPXV has been established as an aerosol transmissible disease using animal challenge studies [7]. Although the latent period of this virus is estimated to be 6 to 13 days, patients can be symptomatic for 2 to 5 weeks and recover without any treatment. The disease initially manifests with fever, headache, fatigue, back pain, muscle soreness, and asthenia. Although monkeypox may initially resemble chickenpox, measles, and smallpox, it can be distinguished by lymphadenopathy. Usually, the disease appears with a fever and within 1-3 days, skin eruption begins. Face and extremities are commonly affected by MPXV rash. In most cases, rash appears on face, oral mucous membranes, and palms and soles of extremities. Sometimes it also involves genitalia, conjunctivae, and cornea. Before desquamation, the pleiomorphic skin lesions evolve through four stages - macules, papules, vesicles, and pustules. However, as lesions may fuse upon enlargement, destruction of large proportions of skin can occur in some cases [11,22–24]. Monkeypox can trigger secondary infections and lead to pneumonia, sepsis, encephalitis, and corneal infection which may result in loss of vision [11,22]. The documented risk factors for severe disease are young age, old age, pregnancy, prolonged viral exposure, poor health status, and underlying immune deficiencies, including diabetes and HIV/AIDS [22,25]. Smallpox vaccination was proven to be protective against MPXV, however, smallpox eradication led to the termination of the global vaccination program and unvaccinated younger populations are considered more susceptible to monkeypox infection [24,26].

Traditional medicine has made use of viral remedies for thousands of years. Ginseng (*Panax ginseng*), "the king of all herbs" was discovered in the mountains of Manchuria, China [27], and belongs to the Araliaceae family. Different clinical, *in vitro* and *in vivo* studies reported that ginseng can enhance resistance to microbial attacks by modulating immune systems [28]. It is evident that ginseng could be useful in treating rotavirus [29], hepatitis virus [30], human immunodeficiency virus (HIV)-1 [31] infection along with the appropriate drugs and vaccines. Possibly, ginseng could be helpful in preventing "monkey pox" infection.

2. Ginseng and the immune system

Innate immunity and adaptive immunity build up the human immune system through the interactive network of organs, cells, and proteins to defend against pathogens and antigens. Innate immunity is the general defense mechanism that reacts right away to any health threats. It incorporates both chemical and physical defenses, including skin, mucous membranes, stomach acid, phagocytes, natural killer cells (NKs), cytokines, inflammatory substances, and bacteriolytic lysozymes found in salvia and tears. Numerous works of research have suggested the importance of ginseng extract in enhancing immunity and immunomodulating actions of different immune system components.

Phagocytic activity of macrophages, the most important components of innate immunity that identify, engulf, and destroy pathogens and apoptotic cells, was boosted up by ginseng extracts and their derivatives [32]. A ginsenoside (prime pharmacological ingredient of ginseng) derivative 20S-dihydroprotopanaxadiol (2H-PPD) reportedly enhanced macrophage phagocytic activity, ROS production, and secretion of co-restorative CD80 and CD86 gene in RAW264.7 cells treated with sodium nitroprusside, as well as increased U937 cell and cell combination tempted by CD29 and CD43 antibodies [33]. Ginsenoside Rb1 has also been discovered to promote macrophage phagocytosis via the p38 mitogen-triggered protein kinase/Akt pathway [34], and by adjusting NF-κB and mTOR signaling pathways in RAW264.7 cells [35]. In the same cell line, ginsenosides Rg3, Rg5, and Rk1 were also discovered to improve macrophage activation via the ERK/c-Jun pathway [36]. Ginseng polysaccharide, another important ginseng compound, showed similarly enhanced macrophage phagocytosis and cytotoxicity on K562, HL-60, and KG1α cells [37]. Moreover, ginseng oligosaccharides were reported to improve phagocytic action by triggering the JNK, ERK, p38, and NF-κB signaling routes [32]. Various studies demonstrated that aqueous ginseng extract can increase macrophage phagocytosis by enhancing immunomodulating nitric oxide and inducible nitric oxide synthase, cytokines like IL-6, IL-10, IL-12, and TNF, granulocyte-macrophage colony-stimulating factor (GM-CSF), and the chemokines-macrophage chemotactic protein-1 [38–40]. Dendritic cells (DCs) showing antigen-specific immune responses are also an important component of innate immune system along with adaptive immune system [39]. Ginseng polysaccharides were reported to facilitate DCs to raise immunity by regulating T helper cells ratio (Th1/Th2) [41]. Ginsan, a ginseng polysaccharide, significantly induced immunity by the extended secretion of IL-12 and TNF-α, surface expression of CD86, MHC class II, and allogeneic $CD4^+$ T lymphocytes [42]. Acidic ginseng polysaccharides also stimulated growth of bone marrow dendritic cells (BMDCs) through decreasing acid phosphatase-ACP activity, elevating crucial co-stimulatory MHC II, CD80, CD86, CD83, and CD40, and producing more cytokines like IL-12 and less TNF-α [43]. Additionally, ginsenosides Rg6, F4, ST1, SL2, SL3, Rh3, Rk2, and Rs4 from steamed ginseng-flowers and leaves primarily suppressed the generation of IL-12 in lipopolysaccharide induced BMDCs [44]. Natural killer (NK) cell is another vital component of inherent immunity that exhibits robust cytotoxic action to cells under physiological stress like cancer cells and viral-infected cells.

Ginseng extract was found to increase number and activity of NK cells in an animal model [45,46].

Adaptive or developed immune system is customized long-lasting immunity that works from immunologic memory against antigens through precisely controlled interaction between antigen-presenting cells (APCs) and lymphocytes (mainly B cells and T cells). The humoral and cellular immune responses are the two main components of adaptive immunity, and the main participants are B and T cells which are continuously generated from progenitor stem cells in the thymus and bone marrow. In humoral immunity, also called antibody-mediated immunity, antibodies secreted by B cells invade pathogens through phagocytosis, neutralization, and by upregulating complementary activities [47]. Ginseng root extract was found to regulate antibody secretion (increase of IgA and decrease of IgG), serum cytokine levels (increase IL-2, IL-10, and interferon-γ), and NK cell activities which are the key factors of adaptive immunity [48]. Aqueous ginseng extracts exhibited increased antibody production and NK cell activities in both *in vivo* and *in vitro* experiments [49]. An *in vitro* study was conducted to understand the humoral immune response of red ginseng extract (RGE) and found that ginsenoside Rg1 and 20(S)-Rg3 use B cells differently during IgA-production using the specific stimulation of GLTα expression [50]. Cell-mediated immunity activates macrophages and NK-cells, and releases cytolytic T cells as well as different cytokines in reaction to pathogens or antigens rather than generating antibodies. Ginseng was also found to have immunological effects when combined with cyclosporine A (CsA) to differentiate simple T helper and regulatory T cells (Tregs), and to quantify their cytokine secretion utilizing CD4+ T cells agitated with the T cell receptor (TCR) or allogeneic APCs [51]. Ginsenosides extracted from KRG can increase the phorbol-12-myristate-13-acetate (PMA)/Ionomycin (IM)-stimulated T-cell growth regulator IL-2 function of NF-AT cells in EL-4 T cells [52].

In another study, three dammarane triterpenes (1–3), and two formerly unidentified compounds 27-demethyl-(E,E)-20(22),23-dien-3β,6α,12β-trihydroxydammar-25-one (1) and 3β,20(S)-dihydroxydammar-24-en-12β,23β-epoxy-20-O-β-d-glucopyranoside (2) were isolated from Panax ginseng leaves. These dammarane triterpenes (1–3) substantially improved IL-12 expression in LPS-stimulated mice model while formerly unidentified compound 27-demethyl-(E,E)-20(22),23-dien-3β,6α,12β trihydroxydammar-25-one was reported to enhance IL-2, reduce IL-4 and IL-6 expression on Con A-initiated splenocytes [53]. Ginsenosides Rc and Rd have also been found to boost cellular immune response by encouraging T-cell growth, marginally raising NK cell activity, and suppressing the efflux pump for multiple drug resistance [54]. When activated with anti-CD3/anti-CD28 antibodies, ginsenoside Rg1 improves CD4+ T-cell activity and fixes Th1-dominant clinical abnormalities in a dose-dependent manner [55]. Ginseng oligopeptides were able to increase macrophage phagocytosis capability, NK cell action, stimulate T and Th cells, release IL-2, IL-6, and IL-12 and stimulate the formation of IgA, IgG1, and IgG2b [56]. It is obvious from the above discussion that ginseng works efficiently in different ways to enhance immunity that eventually facilitates that fight against diseases.

3. Antiviral activities of ginseng and potential of ginseng in treating monkey pox

Scientists around the world have been looking at a variety of naturally occurring chemical components as potential inhibitors of various viral infections. Ginseng and its extracts are proven to boost immune system in several ways that are beneficial to fight against pathogens like viruses. Viruses impair, alternate, and destroy components of immune system leading to potentially serious consequences during viral diseases. Several *in vitro* and *in vivo* investigations have revealed that ginseng and ginseng derivatives can uphold the host from various virus infections. For instance, ginseng extracts have been identified to improve survival rates by boosting immunity against influenza infection by enhancing immunomodulatory cytokines IFN-α, IFN-γ, and by reducing provocative genetic material (IL-6, IL-8) [57–60]. Ginseng also reportedly increased the levels of antibodies [61] and triggered more immunity component (T cells and NK cells) [62], while inhibiting plaque formation [63] and hemagglutination and neuraminidase activity [64], subsequently contributing to the survival rate.

Several *in vitro* and clinical analyses confirmed that ginseng and its compounds can prolong survival of the host by restricting the depletion of immunomodulatory CD4 T cells due to HIV infection [65–69]. Ginseng extracts can also enhance the elimination of cell replicating *pol* gene (Δ*pol*) [70], accessory protein *nef* gene (gΔnef) of HIV that promotes HIV infection [71], and cytoprotective HIV-1 infested macrophages through preventing PDK-1 phosphorylation and the AKT pathway [72], as well as suppressing immune hyperactivation state by HIV antigen [73].

Ginseng extracts were also found to protect from Respiratory syncytial virus (RSV)-produced cell fatality and viral replication by increasing IFN-γ synthesis, CD8+ T cells and CD11c + DC cell levels, as well as suppressing RSV provoked hostile cytokine genes (IL-6 and IL-8) [74–76]. Some studies found ginseng extract is useful against herpes simplex virus (HSV) as ginseng reduces plaque formation and viral penetration [77], prevents the demise of glioma stem cells [78], reduces medical seriousness, improves survival level and virus-related clearance due to high IFN-γ excretion, amplified mRNA expression of IFN-γ, granzyme B, and the presence of Fas-ligand in the iliac lymph [79]. Red ginseng extract was identified to work against hepatitis A virus (HAV) by reducing the level of HAV titer [80]. While it demonstrated anti-hepatitis B activity by inhibiting c-Jun N-terminal kinase/AP-1 signal, it also degraded TNF receptor-related factor 6/transforming growth factor β activated kinase-1 [81], along with lowering non-invasive fibrosis serologic [82]. Moreover, ginseng polysaccharides, ginsenoside-Rb2 and its hydrolytic product, 20(S)-ginsenoside-Rg3 showed reduction of rotavirus (RV) induced diarrhea by inhibiting attachment of RV to cells [83,84].

Ginsenosides are likely to have an anti-enterovirus 71 effect since they have been shown to decrease carbapenemase-producing enterobacterales (CPE) of enterovirus 71 (EV71)-infected rhabdomyosarcoma (RD) cells and EV71-tempted viral protein-1 (VP-1) expression and to enhance immune responses, type I IFN reactions, and reduce IFN-β [85,86]. Ginsenosides also exhibit substantial antiviral behaviors against coxsackievirus B3 (CVB3) [85]. Ginseng is a prospective aspirant to prevent the SARS-COV-2 virus as it exhibited favorable bond energy (8.618 kcal/mol) for receptor-binding domain of SARS-CoV-2 [87]. Red ginseng root extract (HRG80™ Red Ginseng) was found to fight against COVID-19 as it can diminish the most important symptoms of COVID-19 such as chronic fatigue syndrome and fibromyalgia [88].

Ginseng and its compounds may potentially be appropriate and sought-after therapeutic agents against monkey pox virus (MPV). Usually MPV is very mild, self-regulating, and may not even need any special antiviral drug, but orthodox antiviral medications are usually suggested for serious cases. Proper nursing, pain alleviation, regular hydration and appropriate diet, and prevention of bacterial superinfection of skin lesions constitute the primary treatment for mild cases. Several studies have shown that ginseng is proven for significant analgesic and anti-inflammatory properties [89,90] and anti-bacterial infection activities [91,92]. Historically in China ginseng powder was used as a vaccine against smallpox caused by variola virus, a member of the same family as monkeypox virus

[93]. The prospective efficacy of ginseng is thus largely anticipated for the treatment of monkey pox. Detailed information of ginseng and its component activities against different viral infections are tabulated in Table 1.

Table 1
Anti-viral Activities of Ginseng and Its Component Against various of Viral Infections

Virus Name	Strain	Ginseng or its compounds	Type of work	Benefits	Ref.
Influenza Virus	Influenza a virus	Red ginseng extract (RGE)	*In vivo* and *in vitro*	Higher survival of epithelial cells, release of immunomodulatory cytokine IFN-γ, pro-inflammatory IL-6, IL-8, and inhibits the permeation of provocative cells into the respiratory lumens.	[57]
	H1N1 and H3N2	*Panax ginseng* polysaccharide	*In vivo*	Improves survival rates and heterosubtypic lethal challenge and reduces IL-6	[58]
	Influenza virus A (PR8)	Ginseng extract	*In vivo*	Boosts antibodies levels	[94]
	H1N1 and H3N2 influenza viruses	Korean red ginseng extract	*In vivo* and *in vitro*	Improves immunity, and restricts growth of virus	[59]
	H1N1, H3N2, H5N1, and H7N9	Fermented ginseng extracts	*In vivo* and *in vitro*	Neutralizes virus by preventing hemagglutination coupled with neuraminidase activity and retard secondary infection	[64]
	H5N1 influenza virus	Red Ginseng	*In vivo*	Increases secretion of immunomodulatory IFN-α and -γ	[60]
	Influenza A (H1N1) Virus	Korean Red Ginseng	*In vivo*	High survival rate for the inhibition of plaque formation, and body weight loss	[63]
	H5N1 Avian Influenza Virus	Ginseng polysaccharides (APS, GPS)	*In vivo*	Improves antibody levels and the expression of cytokines that enhance H5N1 vaccine response	[61]
	H1N1	Red ginseng	Cell work (PBMC)	Better activation of T and NK cells, in addition to lower progression of viral lytic cycle and lung infection which consequently improves the survival rate	[62]
Human immunodeficiency virus (HIV)	HIV-1	KRG	Cell work (PBMC)	Maintenance of CD4+ T cell amounts combined with delayed aversion to Zidovudine	[65]
	HIV-1	Ginseng triterpenoids	Cell work (HIV protease enzyme)	Inhibition of HIV-1 protease with IC50-10.5, 10.3, 12.3 and 6.3 μM.	[95]
	HIV-1	KRG	Cell work (HIV-1 env genes from blood samples)	Extension of R5 continuance interval through growing false positive rate, thus decelerating the coreceptor adjustment.	[96]
	HIV-1	KRG	Clinical analysis	Surge of survival rate by reducing the depletion rate of CD4 T cell	[66–69]
	HIV-1 subtype B	KRG	Cell work (Nef genes amplified from PBMC) and clinical analysis	High incidence of significant deletion in the*nef*gene (gΔnef)	[71,97,98]
	HIV-1 subtype B	KRG	Clinical analysis	Excellent internal elimination in the*pol* gene (Δ*pol*),	[70]
	HIV-1	KRG	Clinical analysis	Inhibition of immune hyperactivation state by HIV antigen	[73]
	HIV-1 (D3)	Ginsenoside	Clinical analysis	Elimination of cytoprotective macrophages, inhibition of AKT and glycogen synthase kinase-3β phosphorylation in the D3-transduced macrophages, eradication of the cytoprotective CHME5 cells expressing HIV-1 tat	[72]
Respiratory Syncytial Virus (RSV)	RSV	Panax Korean Red Ginseng	*In vitro* and *in vivo*	Increases the endurance of lung epithelial cells, stops viral replication, suppresses IL-6, IL-8, and ROS generation, enhances IFN-γ-releasing DCs	[74]
	RSV	Red ginseng	*In vitro* and *in vivo*	Impedes HEp2 cells death, viral replication, generation of cytokines TNF-α, loss of body weight, and increased secretion of IFN-γ, $CD8^+$ T and $CD11c^+$ DC cells	[75]
	Formalin-inactivated-RSV	Ginseng	*In vivo*	Enhances IgG2a isotype antibody and Th1 immune responses that regulate CD3 T-cell counts, reduces weight loss, IL-4 secretion, and raises IFN-γ excretion.	[76]
Herpes simplex virus	HSV-1 and HSV-2	Notoginseng	*In vitro*	Reduction of plaque as well as viral penetration	[77]
	HSV-1	Ginsenoside Rb1	*In vitro*	Stimulation of cell growth, inhibits death of glioma cells and neuronal cells	[78]
	HSV-1	Red ginseng	*In vivo*	Reduces infection, medical seriousness and upsurges survival value and viral clearance for high IFN-γ discharge, enhances mRNA expression of IFN-γ, granzyme B, and Fas-ligand in the iliac lymph	[79]
Hepatitis Virus	Hepatitis A Virus	Red ginseng	Cell work	Notably reduces the virus titer	[80]
	Hepatitis B	Red ginseng	Clinical analysis	Lowers the non-invasive fibrosis serologic	[81]
	Hepatitis B	Ginsenoside	Cell work	Reduction of TNF receptor-associated factor 6/transforming growth factor β activated kinase-1 and impedes the c-Jun N-terminal kinase/AP-1 signaling	[82]
Rotavirus (RV)	RV	Ginseng Polysaccharides	*In vitro*	Stops viral attachment to cells	[83]
	RV	Korean Red Ginseng	*In vivo*	Significant reduction of RV-induced diarrhea	[84]
Enterovirus 71 (EV71)	EV71	Ginsenoside	Cell work	Antiviral activity is comparable to antiviral drug ribavirin	[85]
	EV71	Ginsenoside	*In vitro* and *in vivo*		[86]

Table 1 (*continued*)

Virus Name	Strain	Ginseng or its compounds	Type of work	Benefits	Ref.
				Reduces CPE of EV71-infected RD cells and EV71-induced VP-1 expression, results in high immune responses, Type I IFN responses and IFN-β reduction changes the resistance to virus	
Miscellaneous	SARSCoV-2	Floralginsenoside B	Simulation	Satisfactory binding affinity (8.618 kcal/mol) with the receptor-binding domain of SARS-CoV-2	[99]
	Coxsackie virus B3	Ginsenoside	Cell work	Exhibits significant resistance to virus	[85]
	Human rhinovirus 3	Ginsenosides	Cell Work	Substantial antiviral activities	[85]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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