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Review Article

Potential application of ginseng in sepsis: Applications of ginseng in sepsis

Fuxun Yang [1], Jiajia Li [1], Yunping Lan, Yu Lei, Fan Zeng, Xiaobo Huang, Xiaoxiu Luo*, Rongan Liu*

Department of ICU, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China

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ABSTRACT

Sepsis and septic shock affect millions of people worldwide each year with high clinical mortality rates. At present, basic research on sepsis has emerged in an endless stream, but there are few effective clinical translation results. Ginseng, a medicinal and edible representative of Araliaceae plants, contains a variety of biologically active compounds including ginsenosides, alkaloids, glycosides, polysaccharides, and polypeptides. Neuromodulation, anticancer activity, blood lipid regulation, and antithrombotic activity have been linked to ginseng treatment. At present, basic and clinical research have suggested various applications of ginseng in sepsis. In view of the different effects of various ginseng components on the pathogenesis of sepsis, and in order to further understand and develop the possible value of ginseng in sepsis, this manuscript reviews the application of various components of ginseng in the treatment of sepsis in recent years.

1. Introduction

Sepsis is an infection-induced dysregulated host response that results in hemodynamic disturbances and multiple organ dysfunction. Sepsis and septic shock affect millions of people worldwide each year, and patients with septic shock often face death. The sepsis rate is as high as 30%, and early identification and appropriate management are critical for improving disease prognosis [1]. The pathophysiological mechanisms underlying sepsis are complex and involve inflammation, immune regulation, coagulation disorders, neurological/endocrine disorders, and epigenetic regulation. Long-term sepsis can lead to tissue injury, metabolic acidosis, hypotension, multiple organ dysfunction, and even death [2]. Therefore, identifying effective targets for sepsis treatment has always been a focal issue pursued by researchers. Although basic research on sepsis has been actively carried out in recent years, the heterogeneity of this research is high, and many results are still controversial, so the clinical translation value is low [3].

Ginseng is the dry root and rhizome of Panax ginseng Meyer, a traditional plant and food product, and its distribution in the world is mostly concentrated in South Korea, China, and other Asian regions. It contains a variety of biologically active compounds, including ginsenosides, alkaloids, glycosides, polysaccharides, and polypeptides, which have shown anti-aging, anti-diabetic, immunomodulatory, neuromodulatory, anticancer, blood lipid regulation, and antithrombotic activities [4]. At present, basic and clinical research have suggested the application of ginseng in sepsis. In view of the different effects of various ginseng components on the pathogenesis of sepsis, and in order to further understand and develop the possible value of ginseng in sepsis, this paper reviews the application of various components of ginseng in the treatment of sepsis in recent years (Fig. 1).

1.1. Anti-inflammatory effect

Sepsis has a high mortality rate, and the infection-induced host response may lead to rapid disease progression. In the early stages of the disease, the patient is in a hyper-inflammatory stage of shock, high fever, and high metabolism [5]. It is important to control the early inflammatory response, to prevent it from becoming dysregulated and possibly leading to immunosuppression.

The anti-inflammatory effects of ginseng have been demonstrated in various diseases [6,7]. In a 2015 study, intraperitoneal

* Corresponding authors. 32 West Second Section, First Ring Road, Qingyang District, Chengdu, Sichuan, China.
E-mail addresses: 395529832@qq.com (X. Luo), 35279240@qq.com (R. Liu).
[1] These authors have contributed equally to this work.

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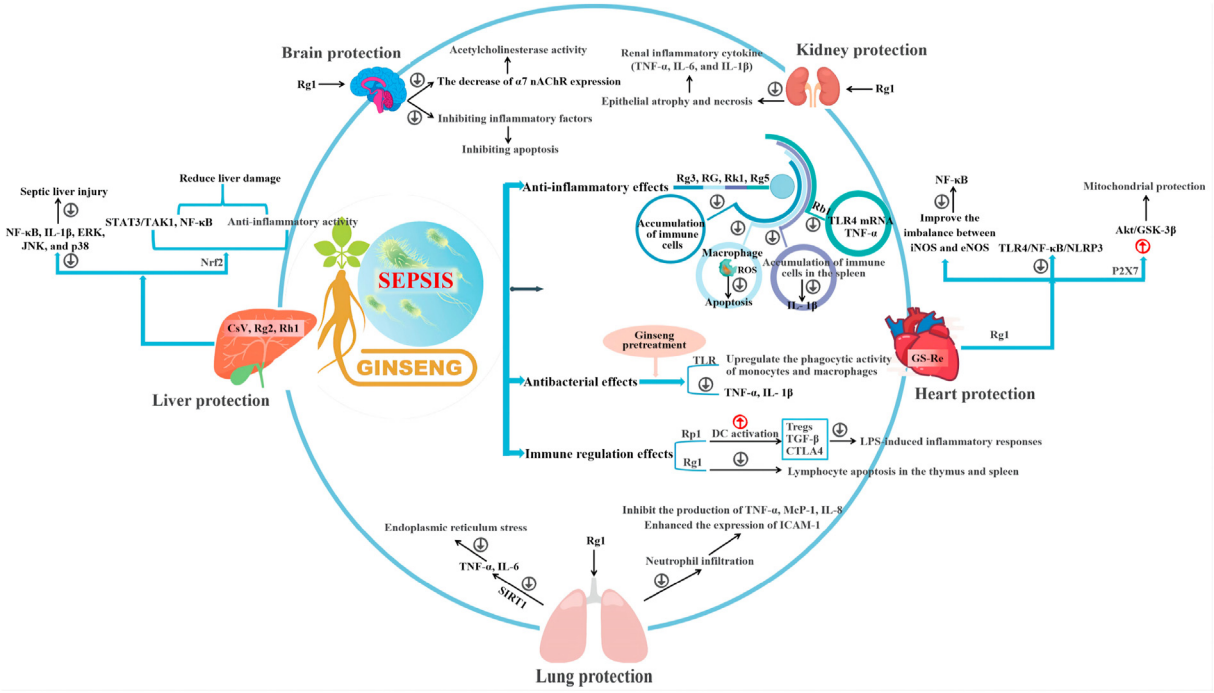

Fig. 1. Different effects of various ginseng components on the pathogenesis of sepsis.

injection of the ginsenoside Rg3 (10 mg/kg) inhibited IL-1β production by reducing nitric oxide levels, thereby inhibiting S-nitrosylation of the NLRP3 inflammasome and increasing the survival rate of septic mice [8]. Rg3 also showed inhibitory effects on LPS- or UV-irradiated-induced reactive oxygen species (ROS) levels in macrophages and HaCaT cells, in turn preventing mouse splenocyte apoptosis [8]. Kim et al. also found that Rg3 (10 mg/kg) attenuated LPS-induced splenomegaly and the accumulation of immune cells in the spleen and reduced serum IL- 1β level [9]. In addition, oral administration of Korean Red Ginseng (50 and 200 mg/kg) [10] and oral administration of Compound K (30–50 mg/kg) [11]a rare component of ginseng, can reduce the inflammatory response in a dose-dependent manner, The mice in these studies were protected from LPS-induced endotoxic shock.

Dysregulated host responses such as hypotension, hypomagnesemia, acidosis, and oxidative stress were observed in LPS-induced sepsis in rats, and pre-administration of 2 mL (0.66 mg/mL) of Korean Red Ginseng (RG) was effective in restoring homeostasis [12]. The downregulation of Toll Like Receptor 4 (TLR4) mRNA expression and inhibition of TNF-α production by Rb1, another ginsenoside, may play a role in the correction of electrolyte imbalance and organ damage in sepsis, improvements in circulation, and protection of organ function [12].

Previous studies have shown that high-mobility group protein B1 (HMGB1) plays an important role in the occurrence and development of sepsis [2]. RK1 and Rg5, the main components of black ginseng, reduce the release of high mobility group B1 (HMGB1) from LPS-activated HUVECs (human umbilical vein endothelial cells) through sirtuin 1 (SIRT1)-mediated HMGB1 deacetylation; RK1 and Rg5 also inhibit sepsis-mediated HMGB1 release and receptor expression, and increase barrier integrity through HMGB1-mediated barrier breakage [13]. In addition, Rb1 has been shown to reduce the leukocyte adhesion and migration of HUVECs. A subsequent cecal ligation and puncture (CLP) mouse model confirmed that Rb1 could reduce mortality and lung injury in septic animals by inhibiting the release of HMGB1 [14]. In addition to the leaf of ginseng playing a role in inhibiting HMGB1, 50 mg/kg ginseng leaf extract injection has been shown to protect septic mice from death through the NO-HMGB1 pathway [13].

At present, there are no clear studies comparing which ginseng components are more beneficial for the treatment of sepsis. However, in the study of Huynh et al. [15], ginsenosides Rg2 and Rh1 treatment may be more effective than single-component treatment; similarly, in another study, when Rg1 and Re were combined to treat septic mice, this combination was found to be able to effectively reduce LPS-induced high body temperature, white blood cell count, and serum levels of pro-inflammatory mediators, and even increased the survival rate of mice with lethal levels of septic shock by 90% [16]. Subsequent analysis showed that due to the different locations of distribution of the different components (Rg1 located intracellularly and extracellularly and Re located extracellularly), the combination of the two components exerted an effective anti-inflammatory effect [16], suggesting that the combination of different components of ginseng may show better efficacy.

1.2. Antibacterial effect

The 2021 edition of the management guidelines for sepsis and septic shock recommends antibacterial treatment for suspected sepsis or early septic shock [1]. There have also been many reports of ginseng as a plant-based antibacterial drug in the past [17,18]. The *Staphylococcus aureus*-induced sepsis model has been the most studied for the antibacterial activity of ginseng. On the one hand, ginseng can reduce the synthesis of inflammatory factors IL2 and IL4 by downregulating TLR transmission in the early stage of bacterial infection [19]. At the same time, ginseng can effectively upregulate the phagocytic activity of monocytes and macrophages to protect animals from fatal sepsis [19,20]. In a mouse model of sepsis caused by *Streptococcus pneumoniae*, treatment with Korean Red Ginseng (100 mg/kg) for 15 days in advance can reduce inflammatory factors TNF-α and IL-1β, his treatment also increased

the clearance rate of bacteria, improving the survival rate of the mice [21].

1.3. Immune regulation effect

In the early stages of sepsis, a large number of immune cells are activated, forming an inflammatory cascade that leads to shock and organ failure. As the disease progresses, the immune system gradually enters a state of exhaustion, which is the key reason for the persistence of the primary infection and the occurrence of superinfection [22]. Abnormal numbers and dysregulation of Tregs are the main causes of immune paralysis. Study has shown that the number of peripheral circulating Tregs in patients with sepsis is increased, regulatory function is enhanced, and that this activity is closely related to the severity of the disease [23]. In mice with sepsis induced by intraperitoneal injection of LPS, after being fed Rp1 (10 mg/kg), mice exhibited dendritic cell activation to upregulate Tregs and upregulated the expression of TGF-β and CTLA4 bound to CD80 and CD86, suppressing LPS-induced inflammatory responses [24]. In Zou et al.'s study, after 20 mg/kg Rg1 was intravenously administered to CLP mice, the mice experienced an increase in peritoneal neutrophil counts [25]. At the same time, the application of ginsenosides could inhibit lymphocyte apoptosis in the thymus and spleen, thereby improving bacterial clearance and survival, suggesting that Rg1 may enhance innate immunity and encourage maintenance of adaptive immunity, providing effective protection against sepsis [25].

1.4. Organ protective effect

1.4.1. Heart protection

Sepsis cardiomyopathy is non-ischemic myocardial dysfunction that occurs in patients with sepsis and is characterized by left ventricular dilation with normal or reduced filling pressure, reduced ventricular contractility, right ventricular dysfunction, left ventricular (systolic or diastolic) dysfunction, and a decreased response to volume infusion [26]. Septic cardiomyopathy occurs as a result of a combination of many factors, which may be related to myocardial inhibitors, mitochondrial dysfunction, oxidative stress, calcium regulation imbalance, apoptosis, adrenergic receptors, and others [27]. Wu et al.'s study also showed that oral North American ginseng pretreatment inhibited the nox2-ErK1/2-TNF-α signaling pathway and improved endotoxemia cardiac function [28]. Luo et al. induced sepsis-induced cardiac dysfunction in male rats by intraperitoneal injection of LPS and found that intraperitoneal injection of Rg1 effectively improved cardiac dysfunction by blocking the TLR4/NF-κB/NLRP3 pathway [29]. The co-culture of cardiomyocytes isolated from neonatal mice with LPS and Rg1 also supported Rg1's reduction in lipopolysaccharide (LPS)-induced apoptosis and inflammation.

The P2X purine receptor 7 (P2X7) receptor is an ATP-gated ion channel expressed primarily in immune cells and plays a key role in inflammatory processes [30]. Intervention with Rg1 (intraperitoneal injection of 35 or 70 mg/kg) in CLP mouse models not only prolonged survival but also activated the Akt/GSK-3β pathway via the P2X7 receptor, inhibiting septicemic cardiac and mitochondrial dysfunction [31].

Ginsenoside Re (GS-RE) is one of the most abundant components of ginseng. In a study by Lopez et al., sepsis was induced by intraperitoneal injection of LPS, and GS-Re preconditioning (15 mg/kg one week in advance) significantly prevented cardiac dysfunction induced by LPS. GS-Re also improved the imbalance between iNOS and eNOS and prevented NF-κB activation and subsequent myocardial inflammation in endotoxemia mice [32]. In addition, the protective effect of GS-Re was found to be closely related to NF-κB, ER, PI3K, AKT, and other related signaling pathways of inflammatory response [32], and further studies are needed to clarify the further mechanism.

1.4.2. Lung protection

The pathological changes associated with acute lung injury in sepsis mainly include three stages: early inflammatory exudation, subacute histopathological hyperplasia, and advanced fibrosis. After effective treatment, most patients see inflammation subside, and slow absorption of edema occurs in the first two stages. However, in the septic shock stage, pulmonary tissue perfusion gradually decreases, pulmonary capillaries shrink, and pulmonary ventilation/perfusion imbalance worsens, often causing irreversible damage to organs and even death [33]. SIRT1 is part of a group of histone deacetylases (HDACs) found in recent years that are dependent on nicotinamide adenine dinucleotide (NAD+) and are located in the nucleus. SIRT1 is activated through acetylation and shows obvious anti-inflammatory effects through the deacetylation of inflammation-related transcription factors [34,35]. In the study of Wang et al., after establishing sepsis models in CLP mice, Rg1 was used to inhibit inflammatory factors such as TNF-α and IL-6 by upregulating SIRT1 expression and reducing endoplasmic reticulum stress, thereby alleviating lung injury in mice; the in vitro studies further supported these results [36].

In a rat septic lung injury model induced by intravenous administration with LPS, ginsenoside Rb1 (10 mg/kg-20 mg/kg) reduced pulmonary edema with neutrophil infiltration and hemorrhage and decreased the lung dry-wet ratio and the number of MPO-positive cells. Rb1 showed the ability to inhibit the production of inflammatory markers such as TNF-α, McP-1, and IL-8 [37]. Expression of ICAM-1, which is an important adhesion molecule for neutrophil activation, markedly increased in the vascular endothelium after LPS infusion [38]. Rb1 significantly reduces the LPS-induced increase in ICM-1 [37].In vitro co-culture of Rb1 with LPS-stimulated pulmonary microvascular endothelial cells (PMVECs) also reduced the increased release of NF-κB p65 and its subsequent translocation to the PMVEC nucleus [37].

1.4.3. Kidney protection

Sepsis is associated with up to 50% of acute kidney injury (AKI) cases, and up to 60% of sepsis patients have AKI. Although the pathophysiological mechanisms are still not fully understood, the harmful inflammatory cascade characteristic of sepsis appears to contribute to AKI [39]. Patients with sepsis and AKI had a significant increase in mortality compared to patients without AKI [39]. In addition, there was a significant increase in mortality in patients with sepsis-associated AKI compared to that in patients with other causes of AKI [39]. In a study by Chen et al., panaxadiolsaponin (PDS) (25.0 mg/kg) and dexamethasone inhibited the formation of reactive nitrogen oxides by inhibiting the NF-κB signaling pathway, reduced the production and release of pro-inflammatory cytokines TNF-α and IL-6, and upregulated the activity of superoxide dismutase (SOD). PDS was better than dexamethasone at inhibiting TNF production, promoting SOD activity, and inhibiting IKB phosphorylation [40].

As an important anti-inflammatory component of ginseng, Rb1 not only improved the survival rate of mice in the LPS injection-induced sepsis mouse model, but Rb1 (5, 10 and 20 mg/kg, ip) pretreatment also significantly alleviated the LPS-related epithelial atrophy and necrosis, interstitial edema, reduced renal inflammatory cytokine levels (TNF-α, IL-6, and IL-1β), thereby ameliorating sepsis-induced renal injury [41].

1.4.4. Liver protection

The liver plays an important role in human metabolism and immune homeostasis and has many important functions, such as detoxification, storage, energy production, nutrient conversion, regulation of hormone balance, and participation in the coagulation process. Liver injury seriously affects the severity and prognosis of sepsis [42,43]. The incidence of liver dysfunction in sepsis patients is 34%–46%, and the incidence of liver failure is 1.3%–22% [44]. Liver dysfunction and failure can directly lead to the progression of sepsis and death in patients [45,46]. Ginseng research on liver disease has focused on chronic liver disease; however, some experiments have shown that ginseng also has the potential to treat liver damage caused by sepsis. Ginseng, a potent anti-inflammatory drug, may also play an important role in septic liver injury.

Dai et al. reported that chikusetsusaponin V(CsV) significantly reduced the levels of liver enzymes (alanine aminotransferase and aspartate aminotransferase) in septic mice and improved pathological changes in the liver. CsV can not only reduce the levels of inflammatory factors (TNF-α and IL-1β) in the serum, but also inhibit the mRNA expression of inducible nitric oxide synthase (iNOS), TNF-a and IL-1b [47]. CsV can inhibit the activation of NF-κB by downregulating the levels of phosphorylated NF-κB, IL-1β, ERK, JNK, and p38 in liver tissue, and reduces the level of nuclear NF-κB protein [47], thereby alleviating septic liver injury. Kurland et al. also found that intraperitoneal injection of 20 mg/kg Rg2 and Rh1 induced antioxidant effects through Nrf2 and increased the anti-inflammatory activity through STAT3/TAK1 and NF-κB signaling pathways in liver cells and macrophages, thus protecting liver function [48].

The liver is the organ with the earliest and most serious occurrence of energy metabolism disorders during sepsis. The mitochondria of hepatocytes are important energy metabolism centers in the body. In sepsis, mitochondrial damage to hepatocytes can cause dysfunction of liver energy metabolism and detoxification, leading to liver insufficiency and even liver failure. Ginsenoside Rg3 activates the AMPK signaling pathway to regulate mitochondrial autophagy and ameliorate mitochondrial dysfunction in LPS-induced animal models and human primary hepatocytes, thereby protecting cells and organs from sepsis [49].

1.4.5. Brain protection

Sepsis can cause acute neurological dysfunction and is referred to as sepsis-associated encephalopathy (SAE) [50]. SAE has been confirmed to occur in 8%–70% of sepsis patients [51]. The pathophysiological mechanisms of SAE have not been fully elucidated, but several commonly accepted mechanisms include impaired cerebral perfusion, altered neurotransmitters, impaired blood-brain barrier, oxidative stress, inflammatory response, apoptosis, microglial activation, and metabolic disorders. Ginsenoside Rg1 can prevent the decrease of α7 nAChR expression, acetylcholine content and the increase of acetylcholinesterase activity in the hippocampal tissue of septic animal models, and improves cognitive function impairment [51]. On the other hand, Rg1 can also protect brain function by inhibiting inflammatory factors in hippocampus and inhibiting apoptosis [52,53]. Kang et al. demonstrated that pretreatment with Rg3 (IG, 20 and 40 mg/kg) effectively improved LPS-induced weight loss, anorexia, and inactivity time. Rg3 attenuated the disturbed turnover of tryptophan and serotonin in the hippocampus, accompanied by decreased mRNA expression of proinflammatory cytokines and indoleamine-2, 3-dioxygenase (IDO) [54]. These core benefits are related in part to microglial activation and the regulation of the NF-κB pathway [54].

1.4.6. Vascular barrier protection

Sepsis is a fulminant systemic inflammatory response involving extensive activation of inflammatory cells and release of inflammatory mediators, resulting in impaired vascular barrier function and increased capillary permeability, in turn leading to extravasation of protein-rich fluids [55]. The intestinal tract is an important barrier for the body to resist external stimuli and plays an important role in absorbing nutrients and preventing bacteria and toxins from entering the body [56–58]. After sepsis, the body experiences flora disorder and an increase in pathogenic bacteria, which produce large amounts of toxins, leading to impairment of intestinal epithelial cells [58–60]. This damages the function of the intestinal barrier, which in turn causes bacterial toxicity of the intestines, introducing toxins into the blood and causing extensive tissue damage; as such, the gut is considered sepsis engine [58–60], and the preservation of intestinal barrier function is necessary.

HMGB1 is considered an advanced mediator of sepsis, and inhibition of HMGB1-mediated severe inflammatory response and restoration of endothelial integrity have become attractive therapeutic strategies for sepsis. Rh1 inhibited the TNF-α, IL-6, NF-κB, and ERK1/2 of HMGB1; Rh1 also inhibited HMGB1-mediated hyperpermeability and leukocyte migration in mice exposed to LPS [60], further improving the survival rate of animals and reducing related organ damage. Lee et al. found that ginsenoside Rh1 significantly reduced the release of HMGB1 in LPS-activated HUVECs [61].

In male Wistar rats, continuous infusion of LPS (5 mg/kg/h) through the left jugular vein for 90 min resulted in increased albumin leakage in mesenteric microveins, which was significantly improved by intravenous administration of Rb1 (5 mg/kg/h). Rb1 also reduced perivascular mortality and intestinal edema. Rb1 ameliorated microvascular hyperpermeability after the onset of endotoxemia, and improved intestinal edema by inhibiting caveolae formation and junction disruption, which was correlated with the suppression of NF-κB and Src activation [62].

1.4.7. Clinical trials

Currently, ginseng is mainly used for compound preparation. Among these preparations, the Shenfu injection and Shenmai injection are the most widely used, but there are no clinical studies on the efficacy of pure ginseng preparation for sepsis. In a prospective study involving 157 people, administration of a ginseng compound preparation effectively increased $CD4^+$ and $CD8^+$ T cells in peripheral blood and upregulated HLA-DR expression in monocytes, but there was no statistical difference in mortality between the two groups [63]. In another study on the Shenfu injection, hemodynamics in the experimental group were more stable, organ protection was more obvious, and mechanical ventilation time and ICU stay time were shortened [64]. Unfortunately, a subsequent clinical trial showed the opposite effect [65]. Therefore, the mechanism of ginseng components in sepsis needs to be supported by more complete basic experiments in the future to realize the application of ginseng from laboratory to bedside.

2. Conclusion

The research related to sepsis has been a hot and difficult issue because of its high morbidity and mortality rate. Despite scientists' continuous exploration in basic and clinical research, there are still no effective interventions to significantly reduce mortality. Ginseng, as an active and effective drug in clinical treatment, has been intensively studied for its active mechanism of ginsenosides and ginseng polysaccharides, and its good efficacy in metabolic diseases and cardiovascular diseases has been clinically proven; ginseng also has beneficial effects in sepsis. A large number of basic

studies suggest that ginseng can exert effective antibacterial, anti-inflammatory, immunomodulatory and organ-protective effects. In the early, middle and even late stages of sepsis, ginseng can play an effective regulatory role and reduce the morbidity and mortality of animal models of sepsis. Ginseng has been used as a compound for sepsis patients and has been found to enhance cellular immunity, improve blood pressure, and reduce lactate levels, and these findings have increased our confidence in ginseng for sepsis treatment. Although ginsenosides with high biological activity are currently difficult to obtain in the natural environment, the preparation of highly active ginsenoside monomers is expected as research on plant tissue culture and reactors has become more sophisticated. More mature ginseng-based products and more basic and clinical studies in the future support the use of ginseng in sepsis.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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