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Short Review

# Roles of ginsenosides in sepsis

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ABSTRACT

The herbal medication Panax ginseng Meyer has widespread use in China, Korea, and other parts of the world. The main constituents of ginseng are ginsenosides, which include over 30 different triterpene saponins. It has been found that ginsenosides and their metabolites including Rg1, compound K, Rb1, Re, Rg3, and Rg5 exert anti-inflammatory activities by binding to the glucocorticoid receptor, modulating inflammation-related signaling, including NF-κB and MAPK signaling, and reducing levels of pro-inflammatory cytokines. Here, we review the recent literature on the molecular actions of ginsenosides in sepsis, suggesting ways in which they may be used to prevent and treat the disease.


## 1. Introduction

Sepsis was recently defined by the “Third International Consensus Definitions for Sepsis and Septic Shock” (Sepsis-3) as a “life-threatening organ dysfunction caused by a dysregulated host response to infection”. Septic shock was further described as sepsis resulting from homeostatic disturbance resulting from injury or infection, leading to high levels of morbidity and mortality [1]. Sepsis is relatively common, estimated as 2.5 cases per 1000 in the western hemisphere, and has been steadily increasing over the past several decades [2,3]. A total of 48.9 million cases occurred in the world in 2017 alone, leading to 11.0 million deaths [4]. For instance, in the USA, a majority of in-hospital deaths result from sepsis, entailing considerable economic costs [5]. A recent study in China found an overall 20.6% incidence and 35.5% 90-day sepsis-related mortality among ICU patients in 44 hospitals, with death rates highest for severe cases [6]. Sepsis is a multifaceted disease and presents with a wide range of symptoms, resulting in difficulties in both diagnosis and treatment. Sepsis may manifest as dysfunction in almost any organ or system, independently of the infection site. Most commonly involved are the heart, kidneys, lungs, liver, central nervous system, and hematological system [7,8]. Severe COVID-19 frequently induces the characteristic symptoms of shock, such as weak pulse and cold extremities, despite an absence of obvious hypotension. Such patients may also show a high degree of metabolic acidosis, suggesting impacts on the microcirculatory system. Patients who's kidneys, liver and lungs have also been affected conform to the Sepsis-3 diagnostic criteria for sepsis and septic shock [9].

The roots and rhizomes of the ginseng plant (*Panax ginseng* Meyer) have long been utilized in traditional Chinese medicine (TCM) as a remedy for sepsis. As documented in the “Encyclopedia of Febrile Diseases” *P. ginseng* decoctions were used to treat disorders such as “a deficiency of qi and loss of qi and weak pulse” and were used in ancient China for treating critically ill patients. Shenfu injection with *P. ginseng* as the main ingredient was listed as the first batch of “National Chinese Medicines for Emergency Departments of Chinese Medicine Hospitals” by the State Administration of TCM. It is currently a commonly used medicine for treating septic shock. The principal active components of *P. ginseng* are ginsenosides which fall into several categories. Dammarane ginsenosides include panaxadiol-type (PPD) compounds that contain a hydrogen atom at C6 (i.e., Rb1, Rb2, Rg3, Rg5, Rh2, and CK) and panaxatriol-type (PPT) compounds containing a sugar at C6 (i.e., Re, Rg1, Rh1); or the oleanane-type (i.e., Ro) [10] (Table 1). *P. ginseng* is usually used alone or combined with other medications for the treatment of inflammation [11,12].

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**Table 1**
Classification of ginsenosides.

| Class | Representative ginsenosides |
|---|---|
| Panaxadiol-type (PPD) | Rb1, Rb2, Rg3, Rg5, Rh2, CK |
| Panaxatriol-type (PPT) | Re, Rg1, Rh1 |
| Oleanane-type | Ro |

This review discusses the pathogenesis of sepsis and its treatment drugs, followed by a summary of known ginsenoside actions and their relevance and potential application to sepsis.

## 2. Pathogenesis of sepsis

Sepsis has a highly complex etiology that is not fully understood, involving impaired immune and inflammatory responses, damage to mitochondria, disruption of hemostasis, and autophagy, amongst other issues, finally leading to organ damage [13]. Imbalances in inflammation are the most critical and are apparent throughout the entire duration of sepsis. Thus, current thinking is that acute inflammation plays a vital part in sepsis pathophysiology, and a full understanding of the process is necessary for effective treatment of the disease.

The innate immune system is activated by pattern recognition receptors (PRRs). Microbial material, including components of bacterial outer membranes such as lipopolysaccharide (LPS), lipoteichoic acid, peptidoglycans, flagellae, fungal mannan, and viral double-stranded RNAs, activate innate immunity [14]. Specific features of these materials, known as pathogen-associated molecular patterns (PAMPs), are recognized by host receptors, including the Toll-like receptors (TLRs), such as TLR4, and NOD-like receptors (NLRs) expressed by immune cells such as macrophages and monocytes [15]. Interactions with TLRs, acting through toll-interleukin-1 receptor homology (TIR) domains on proteins such as myeloid differentiation protein 88 (MyD88) and various tyrosine kinases activates downstream signaling components such as c-Jun *N*-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), and nuclear factor-κB (NF-κB) (Fig. 1) [16]. This signal transduction leads to the NF-κB-induced expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interferon regulatory factor 3 (IRF3), IRF7, or adaptor-protein 1 (AP-1) [17,18]. Cytoplasmic NLRs also contribute to the immune disruption caused by sepsis. These proteins contain nucleotide-binding oligomeric domains (NODs) and LRR domains (similar to TLRs) [19]. The NLRP3 inflammasome may be activated by various factors, including changes in $K^+$ and $Ca^{2+}$ flux and disruption of organelles such as the mitochondria, lysosomes, and trans-Golgi assembly, amongst other cellular disturbances [20]. $K^+$ and $Ca^{2+}$ both play key roles in inflammasome activation [21,22]. NLRP3 activates caspase-1 by cleavage of the precursor which subsequently activates the cytokines IL-1β and IL-18 [23]. Increased levels of these cytokines together with microbial toxins and induced toxicity leads to cell death and the associated release of damage-associated molecular patterns (DAMPs) which, together with PAMPs, are able to activate PRRs [24]. The liver produces significant amounts of high mobility group box 1 (HMGB-1) in endogenous sepsis; HMGB-1 binds and transports LPS via RAGE

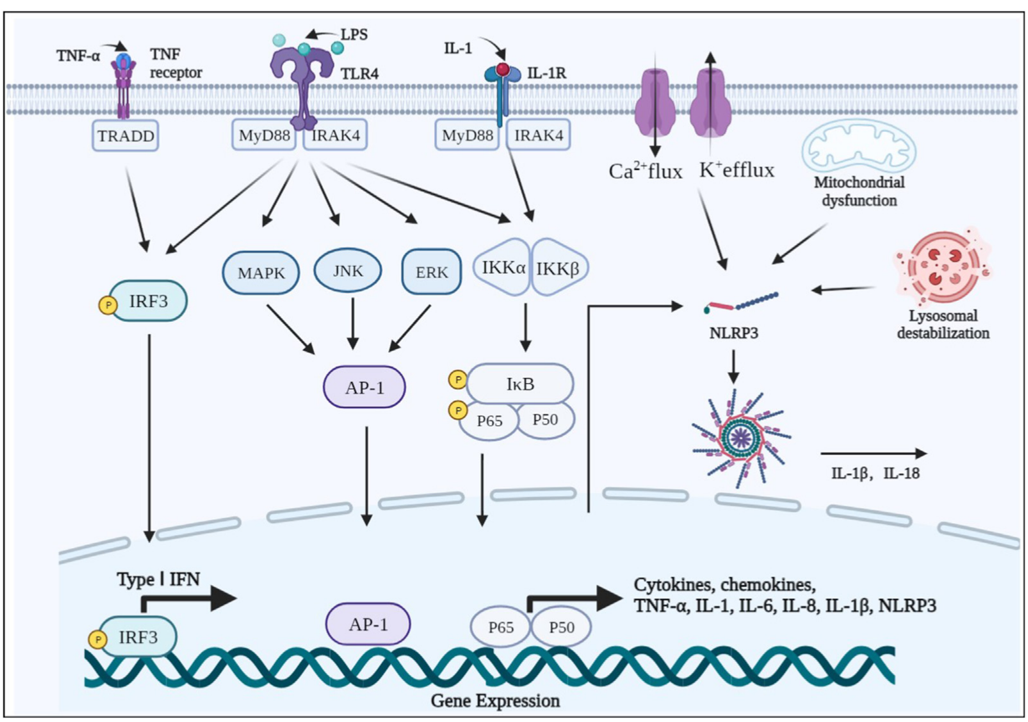


**Fig. 1.** Overview of the pathogenesis of acute inflammation in sepsis.
The binding of PAMPs, including peptidoglycans, flagellin, and LPS, to TLRs activates signaling pathways leading to the recruitment of IRAK4 and MyD88, resulting in IRF3 activation and IFN-I release. Activated TLRs act through MAPK, JNK, and ERK to modulate IKKs (IκB kinases), leading to IκBα phosphorylation. This promotes the release of NF-κB (including p50 and p65) from IκBα, allowing the protein to enter the nucleus where it promotes the expression of pro-inflammatory cytokine and chemokine genes. Inflammation is also enhanced by the secretion of inflammatory factors from cells. In addition, changes in $K^+$ and $Ca^{2+}$ flux and disruption of organelles such as the mitochondria, lysosomes, and trans-Golgi assembly, amongst other cellular disturbances, activate NLRP3 leading to formation of the inflammasome, ultimately leading to increased secretion of IL-18 and IL-1β.
LPS, lipopolysaccharide; TLR-4, Toll-like receptor 4; IL, interleukin; TNFα, tumor necrosis factor-alpha; Myd88, myeloid differentiation primary response 88 protein; IRAK4, interleukin-1 receptor-associated kinase 4; IKK, IκB, kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated protein kinases; JNK, c-Jun *N*-terminal kinase; IRF3, Interferon regulatory factor 3; AP-1, activator protein-1; NLRP3, NOD-like receptor protein 3.

receptors on the surfaces of macrophages and vascular endothelial cells, ultimately leading to the induction of cellular pyroptosis, damaging organs and leading to possible shock and death [25,26]. Cytokine storms appear to account for much of the pathology of COVID-19. Cytokines are expressed by immune cells and epithelial cells of the lung during influenza, mediated by PRRs and NLRs. COVID-19 patients typically show raised levels of pro-inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6 [27,28].

## 3. Specific drugs for treating sepsis

Numerous clinical studies have addressed the issue of sepsis treatment. Antibiotics and fluid resuscitative therapies are available as effective treatments for sepsis [29] while antimicrobial therapy is the foundation of treatment [30]. In addition, glucocorticoids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are used as adjuvant therapy [31,32]. Candidate treatments may be classified into three types, namely, treatments for purifying the blood, those that modulate the immune response, and therapies that target other systems (Table 2) [33].

However, apart from antibiotics and vasopressors, there is no specific effective drug therapy for sepsis. Septic shock has long been managed by using synthetic steroids as adjuvant treatments. GCs, in particular, are widely used and are highly effective for suppressing immune activity and reducing inflammation. Their first reported use for reducing sepsis mortality was in 1976. Low- and medium-dose GCs for reducing septic shock have been included in the “sepsis/septic shock emergency treatment” guidelines [34]. In recent decades, however, the clinical usefulness of GCs for the treatment of sepsis has been disputed. Twenty-two randomized placebo-controlled trials published until 2017 have investigated the efficacy of GCs in sepsis treatment, with inconsistent findings [35]. In 2018, two clinical trials, both published in the *New England Journal of Medicine*, reported contrary findings on the efficacy of GCs in reducing sepsis-related death [36,37]. Although GCs affect the inflammatory response to sepsis, the efficacy of treatment in patients with sepsis is uncertain. GCs bind to the GC receptors, NR3C1 which dissociated from proteins such as HSP90, and then translocated to the nucleus after phosphorylation and dimerization, where it binds specifically to transcription factors (NF-kB, AP-1), blocking their transcriptional activity to exert anti-inflammatory and anti-shock effects [38–40]. It also binds to GC-responsive elements (GREs) in DNA, activating the expression of genes encoding anti-inflammatory factors such as GILZ, Anx-1, and MKP-1, inhibiting the MAPK inflammation pathway and lowering inflammation [41]. A lack of GC sensitivity, also known as GC resistance (GCR) has been reported in between 4% and 10% of asthma patients and 30% of patients with rheumatoid arthritis, while close to 100% of sepsis patients show GCR [41,42]. The mechanism underlying GC resistance is related to the glucocorticoid receptor (GR) expression levels (GR transcription, translation, and degradation) and dysfunctional processes (receptor subtypes, nuclear translocation, transcription activation, and suppression). GCR caused by abnormal GR expression has significant effects on GC action in the treatment of sepsis [42]. Establishing the roles of GCs and GR could provide a solution to the undetermined anti-inflammatory effects of GCs.

## 4. Anti-sepsis effects of ginsenosides

TCM has unique advantages for the treatment of sepsis, and many Chinese medicine prescriptions use *P. ginseng*, indicative of the value of *P. ginseng* in sepsis treatment. Specifically, ginsenosides, as the main *P. ginseng* components, may have particular benefits for sepsis treatment (Table 3).

### *4.1. Ginsenosides Rb1 and Rb2*

P. ginseng is frequently used as a traditional treatment in Asia, and Rb1 is the principal ginsenoside component [43]. Rb1 has been found to protect against liver and lung injury, including pulmonary edema, induced by sepsis. Its effects on inflammation appear to occur largely by modulating NF-κB activity. Rb1 significantly attenuated the mRNA levels of TLR4 and inflammatory factors, especially NF-κB p65, in the lung, reducing the levels of IL-1β, IL-6, and TNF-α [44]. Dose-dependently, both, Rb1 and Rb2, significantly reduced TNF-α and IL-6 levels [45]. Besides, Rb1 was also observed to reduce p65, ERK, and JNK phosphorylation, as well as inhibiting TLR2 activity [46]. These findings suggest that Rb1 may act by reducing the activity of NF-κB. In a rat model of septic shock, Rb1 was observed to protect the lung and liver, normalize blood pressure, and enhance survival by inhibiting NF-κB and TNF-α production [44,47,48].

### *4.2. Ginsenoside Re*

Protopanaxatriol ginsenoside Re is often used as an anti-inflammatory agent. Re has been found to reduce inflammation in revulsive primary hepatocytes and RAW264.7 cells and may also inhibit IKK-β [49] by blocking its phosphorylation, together with blocking NF-κB activation and lowering the levels of pro-inflammatory proteins such as COX-2, iNOS, TNF-α, IL-1β, and IL-6, and NO production. In addition, Re prevented phosphorylation of IRAK-1 and degradation of IRAK-4, as well as the TLR-LPS interaction [50], and also inhibited phosphorylation of several MAPK-associated proteins, including c-JNK, ERK1/2, and p38, and the NF-κB-associated proteins p65 and IκB [51]. Sepsis and septic shock

**Table 2**
Summary of recent new drug candidates in sepsis.

| Drugs | Structure | Dosage | Mechanism | Ref. |
|---|---|---|---|---|
| MEDI4893 | Human immunoglobulin | 225, 750, 2250, 5000 mg | Binds *S. aureus* alpha toxin with a high affinity | [94] |
| MEDI3902 | Human immunoglobulin | 250, 750, 1500 or 3000 mg, i.v.drip | Bind to both the PcrV protein and Psl exopolysaccharide on the surface of *P. aeruginosa* | [95] |
| ART-123 | Human soluble thrombomodulin | 0.06 − 6 mg/kg/d, i.v.drip | Change thrombin substrate specificity from pro-coagulant to anti-coagulant activity through the activation of protein C | [96] |
| Adrenomedullin | Short half-life free circulating peptide | 2, 4 mg/kg, i.v.drip | Reinforce the endothelial barrier and reduce sepsis-induced vascular leakage | [97] |
| GM-CSF | Recombinant human granulocyte-macrophage colony-stimulating factor | 4 μg/kg/day, i.c. | Stimulate the production, maturation, and function of monocytes/macrophages and neutrophils | [98] |
| Nangibotide | Synthetic TREM-1 antagonistic peptide | 0.3, 1.0, 3.0 mg/kg/h, i.v.drip | Decrease leukocyte activation and innate immune response | [99] |
| CYT-107 | Pluripotent cytokine | 10 μg/kg, once a week or twice a week | Reverse sepsis-induced lymphopenia and avoid excessive inflammatory response | [100] |

**Table 3**
Summary of the therapeutic effects of ginsenoside against sepsis.

| Ginsenoside | Dosage and administration route | Effects | Experimental models | Ref. |
|---|---|---|---|---|
| Rb1 | 5 mg/kg/h 60 min, i.v. | Decrease of NF-κB activity and proinflammatory molecules | LPS-induced ALI in male Wistar rats | [44] |
| | 20 mg/kg, i.g. | Inhibit IL-1β, IL-6 and TNF-α production | (*S. aureus*)-induced ALI in Kunming male mice | [47] |
| | 40 mg/kg, i.g. | Downregulate the expression of TLR4 mRNA and inhibited the production of TNF-α | septic shock in SD rats | [48] |
| Rb2 | / | Inhibit TNF-α and IL-6 production | LPS-stimulated RAW 264.7 cells | [45] |
| Re | 10, 20 mg/kg, i.g. | Inhibit the expression of proinflammatory cytokines TNF-α and IL-1β | LPS-induced inflammation in male ICR mice | [50] |
| | 20 mg/kg, i.g. | Prevent NF-κB and MAPK activation | LPS-induced ALI in male ICR mice | [53] |
| CK | 20, 30, 40 μM | suppressed phosphorylation of IκB-α and NF-κB, MAPK activation | LPS-treated RAW264.7 cells | [54] |
| | 50 mg/kg, 3 d, i.g. | Reduced the levels of inflammatory cytokines TNF-α and IL-6 | Endotoxin-induced lethal shock in male C57BL/6 mice | [56] |
| Rh1 | 10, 25, 50 μM | inhibited iNOS, COX-2 protein expression and the activation of NF-κB | LPS-treated RAW264.7 cells | [58] |
| | 126 or 252 μg/mouse, i.v.) | Suppressed the production of TNF-α, IL-6, activation of NF-κB and ERK 1/2 by HMGB1 | CLP model in male C57BL/6 mice | [62] |
| | DEX (1 μM) with Rh1 (10 μM, 1 μM, 0.1 μM) | Inhibit the transcription of pro-inflammatory genes via suppression of the transcriptional activation induced by AP-1 and NFκB | RAW264.7 cells | [61] |
| Rh2 | 10, 20, 30 mg/kg, i.g. | blocked iNOS, COX-2, the phosphorylation of IκB-α, ERK, JNK, p38, protein expression | LPS-induced ALI in male ICR mice | [63] |
| Rg1 | 15, 30, 60 mg/kg, i.g. | Inhibit the protein expression of TLR4 and its downstream genes including NF-κB and MAPKs | (LPS/D-GalN)-induced ALI in C57BL/6 mice | [68] |
| | 20 μM | Revers the increased expression of TLR4, NF-κB, and NLRP3 | Neonatal rat cardiomyocytes | [70] |
| | 10 μM | Attenuate NF-κB cytoplasmic-to-nuclear translocation and downregulation of MAPK phosphorylation | RAW264.7 cells | [72] |
| Rg5 | 5, 10 μM | Inhibited the phosphorylation of NF-κB | Male C57BL/6 mice alveolar macrophages | [73] |
| | 10, 20, 40 μM | suppressing the production of TNF-α and IL-6 and the activation of NF-κB and ERK 1/2 | Primary human umbilical vein endothelial cells (HUVECs) | [74] |
| Rg3 | 10 mg/kg, i.g | Inhibit IL-1β production via the S-nitrosylation of the NLRP3 inflammasome | LPS-induced endotoxic shock in male C57BL/6 mice | [76] |
| | 10 mg/kg, 3 d, i.g. | reduced the level of IL-1βand TNF-α production | C57BL/6 J mice | [77] |
| | 10, 20 mg/kg, i.g. | Improve mitochondrial dysfunction | CLP-induced sepsis male C57BL/6 mice | [80] |
| | 10, 20, 30 mg/kg, i.g. | Decrease the levels of pro-inflammatory mediators and increasing the production of anti-inflammatory cytokines | LPS-induced ALI in male C57Bl/6 mice | [81] |

typically reduce myocardial contraction, adversely affecting cardiac function. Re was shown to counteract these effects by specifically influencing NF-κB activation and MAPK signaling [52] with similar findings reported in lung tissue [53]. These results demonstrate the protective influence of Re on both heart and lung function.

### 4.3. Compound K

Compound K(CK)is an Rb1 metabolite produced by bacteria of the microbiome after P. ginseng ingestion. CK reduces inflammation by inhibiting MAPK phosphorylation, NF-κB nuclear translocation, and IκB-α phosphorylation, as well as competitively inhibiting the GC-GR interaction, in LPS-induced inflammation. CK was also shown to block NO production by suppressing iNOS and to reduce COX-2 mRNA and protein expression, as well as that of IL-1β and IL-6 [54]. The compound was also used in conjugation with CopA3 and gold nanoparticles (GNP-CK-CopA3) for targeting LPS-activated RAW264.7 cells, leading to an attenuation of both NF-κB and MAPK signaling [55]. In addition, CK has been reported to ameliorate sepsis by the regulation of TLR4 signaling induced by GR, not only inhibiting NF-κB and MAPK signaling induced by TLR4, together with pro-inflammatory cytokine production, but also competitively inhibiting binding of GR to the synthetic GC dexamethasone, thus activating GRE. This suppression of inflammation-associated gene expression was observed to occur by disrupting p65/interferon regulatory factor complexes. Notably, CK prevented septic shock in LPS-treated mice by reducing their levels of pro-inflammatory cytokines [56].

### 4.4. Ginsenoside Rh1

The protopanaxatriol-type ginsenoside Rh1 is found especially in Korean Red Ginseng. It has been observed to control stress, inflammation, and immune activity, principally through the modulation of NF-κB signaling [57]. Rh1 has been found to inhibit NF-κB and IFN-γ-induced JAK/STAT and ERK signaling, together with influencing the iNOS and COX-2 protein levels [58,59]. In addition, Rh1 blocked NLRP3 and AIM2 inflammasome activation after macrophage-induced inflammation and inhibited both pyroptosis and the production of IL-1β [60]. Rh1 also potentiated the anti-inflammatory actions of dexamethasone without the side effect of hyperglycemia production. Interestingly, the combination of Rh1 and dexamethasone, even after long-term dexamethasone use, significantly reduced the levels of IL-6, IL-17, and TNF-α, with similar effects seen for IL-6 and IL-17 [61]. It has also been suggested that Rh1 may target the sepsis mediator HMGB1, thus suppressing sepsis; Rh1 reduced both TNF-α and IL-6 levels, together with NF-κB and ERK 1/2 activation, by HMGB1, together with reducing HMGB1 secretion after cecal ligation and puncture in animal models, thus reducing both tissue damage and sepsis [62].

### 4.5. Ginsenoside Rh2

Rh2 has significant anti-inflammatory and anti-allergic actions. Anti-inflammatory effects have been assessed in acute lung injury models where it was found that Rh2 protects against injuries caused by LPS. The compound ameliorated the histological damage, as well as reducing the levels of iNOS, COX-2, p38, the pro-inflammatory NO, TNF-α, and IL-1β, phosphorylation of IκB-α,

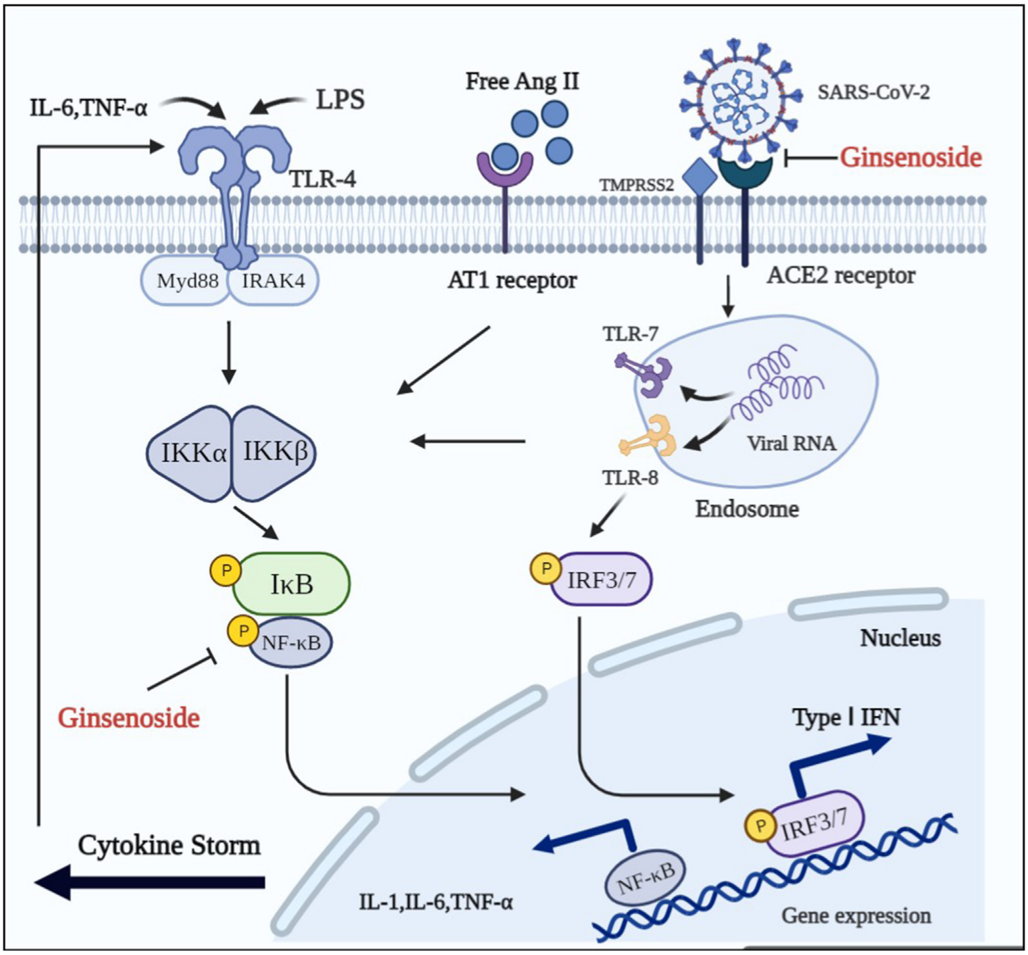


**Fig. 2.** Potential actions of ginsenosides in COVID-19 treatment

The proposed treatment targets NF-κB-mediated signaling that produces the cytokine storm. SARS-CoV-2 interacts with the angiotensin-converting enzyme 2 (ACE2) receptor and undergoes TMPRSS2-mediated endocytosis. The Toll-like receptors TLR7 and TLR8 are activated by the virus's RNA, leading to transcription of interferon-regulator factors (IRFs), such as IRF3 and IRF7. Ginsenosides can block the SARS-CoV-2-ACE2 interaction binding. Endosomal IRFs are also prevented from entering the nucleus, thus inhibiting IFN-I production. TLR activation also triggers, through different intermediates, IKK (IκB kinase) activation, leading to IκBα phosphorylation and the release of NF-κB. Ginsenosides can block this NF-κB activation and subsequent actions in promoting the expression of pro-inflammatory factors, including cytokines, chemokines, and cell adhesion molecules. NF-κB signaling is also promoted by raised levels of free Ang II in the serum resulting from lowered ACE2-induced degradation as a consequence of the interaction between ACE2 and the virus, leading ultimately to the release of IL-6. Thus, NF-κB-mediated inflammation leads to further NF-κB activation, termed the IL-6 amplifier (IL-6 AMP). Ginsenosides inhibit NF-κB signaling, thus lowering the production of pro-inflammatory factors.

SARS-CoV-2, COVID-19; LPS, lipopolysaccharide; Ang II , angiotensin II; TLR-4, Toll-like receptor 4; IL-1, interleukin-1; IL-6, interleukin-6; TNFα, tumor necrosis factor-alpha; Myd88, myeloid differentiation primary response 88 protein; IRAK4, interleukin-1 receptor-associated kinase 4; IKK, IκB kinase; IRF3/7, Interferon regulatory factor 3/7.

ERK, and JNK while promoting the release of anti-inflammatory cytokines (IL-4, IL-6, and IL-10) [63,64]. These anti-inflammatory actions were enhanced by the use of the highly soluble sulfated derivatives, Rh2−B1 and Rh2−B2 [65] which significantly blocked the release of NO, TNF-α, IL-1β, and IL-6, together with reducing MAPK and NF-κB signaling, suggesting that sulfated ginsenosides may have potential for treating sepsis [66].

### *4.6. Ginsenoside Rg1*

Rg1 has been used extensively for the treatment of inflammation and immune-associated disorders [67]. Rg1 is known to protect against lung damage and myocardial disorders resulting from sepsis. The compound significantly reduces the secretion of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and iNOS, while elevating the production of the anti-inflammatory IL-10 [68]. In mouse models, Rg1 was observed to reduce pro-inflammatory cytokine secretion, ameliorating lung damage and increasing survival [69]. Rg1 also enhanced cardiac function and reduced both apoptosis and inflammation in LPS-treated mice, while down-regulating levels of pro-inflammatory cytokines, TLR4, NF-κB, and NLRP3 [70]. The nuclear translocation of NF-κB and p65-DNA binding was reduced, together with MAPK, p38, JNK, and ERK phosphorylation, comparable to the action of dexamethasone. Rg1 is also able to bind GR and can thus augment the anti-inflammatory actions of GCs [71]. The compound also has fewer side effects, and does not promote hyperglycemia, osteoporosis, or immune-related weight loss [72]; it has also been proposed to block inflammasome activation, counteracting both pyroptosis and the raised IL-1β levels [60]. These effects may result from inhibiting the TLR4-NF-κB-NLRP3 pathway.

### *4.7. Ginsenoside Rg5*

Rg5 is one of the principal ingredients of black ginseng. It has been found to block NF-κB activation in LPS-treated alveolar macrophages, together with lowering the levels of the pro-inflammatory cytokines, IL-1β and TNF-α, and the inflammation-associated enzymes COX-2 and iNOS. The compound was also observed to reduce phosphorylation of IRAK-1 and IKK-β, as well as IRAK-1 and IRAK-4 degradation after LPS treatment. Both NF-κB phosphorylation and p65 nuclear translocation were reduced [73] and the production and effects of HMGB1 on leukocytes, tissue damage, and survival in mice were reduced through suppression of TNF-α and IL-6 and the activation of NF-κB and ERK 1/2 [74].

### 4.8. Ginsenosides Rg3 and Rg6

The tetracyclic triterpenoid Rg3 is found in red ginseng. Rg3 acts against inflammation through the MAPK and AMPK pathways together with NLRP3 activation. Rg3 lowers the levels of both NO and reactive oxygen species (ROS), as well as those of TNF-a, IL-1β, and IL-6 [75]. The NLRP3 inflammasome is inhibited by the reduction of S-nitrosylation of NLRP3 by NO [76]. In addition, Rg3 is also able to reduce both IL-1β secretion and caspase-1 activation [77], while promoting phagocytosis of bacteria by macrophages through the ERK1/2 and p38/MAPK pathways [78]. Sepsis frequently leads to mitochondrial damage, which Rg3 can ameliorate by reducing the levels of ROS together with upregulating the expression of transcription factors responsible for promoting the expression of genes responsible for mitochondrial genesis and repair [79]. Rg3 also inhibits apoptosis and can mitigate mitochondrial dysfunction by modulating autophagy through activation of AMPK signaling, and thus protecting against sepsis-induced cellular and organ damage [80]. These findings show that Rg3 protects against lung injury by reducing the levels of pro-inflammatory factors and elevating the levels of factors that reduce inflammation [81].

Coronavirus Disease 2019 (COVID-19) frequently leads to the development of sepsis, and it is thought that the majority of ICU deaths from the disease are sepsis-related [82]. It is worth noting that ginsenosides have potential therapeutic effects on COVID-19. It has been reported that natural compounds, including 20(R)-ginsenoside Rg3, may prevent the entry of viruses, including SARS-CoV-2 [83]. Cytokine storms commonly occur in COVID-19 patients [84] and similar excessive cytokine levels are seen in the peripheral blood mononuclear cells (PBMCs) of the patients [85]. It was found that the use of a PEGylated nanoparticle albumin-bound (PNAB)-steroidal ginsenoside (PNAB-Rg6) lowered the cytokine levels significantly while also reducing the production of pro-inflammatory cytokines by PBMCs. Furthermore, PNAB-Rg6 was also found to reduce the mRNA levels of inflammation-associated genes, such as NRLP3, shown by PCR analysis [86].

Ginsenosides are known to block NF-κB nuclear translocation [87]. IL-6 production is controlled by MAPK/NF-κB signaling [88] and excessively elevated IL-6 is strongly associated with COVID-19 mortality [89]. A key contributor to inflammation is the IL-6 amplifier which, when overactivated, may promote a cytokine storm. This suggests the possibility that blocking the action of the IL-6 amplifier may prevent the cytokine storms seen in severe COVID-19 [90]. In addition, the inflammasome appears to be activated by viral interaction with ACE2, potentially leading to raised inflammation resulting from the activation of inflammatory cascades [91].

Ginsenosides in high concentrations can inhibit the SARS-COV-2-ACE2 interaction, resulting in a reduction in IFN-I production. This suggests a possible use for ginsenosides for COVID-19 therapy (Fig. 2). In addition, ginsenosides can inhibit the activation of inflammasomes to a certain extent. These various signals can connect to a common cascade involving phosphorylation of IκBα in the cytoplasm, resulting in its ubiquitination and subsequent degradation followed by the release and nuclear entry of NF-κB. Ginsenosides act by preventing IκBα degradation, resulting in the retention of NF-κB in the cytoplasm where it is unable to promote the transcription of pro-inflammatory proteins.

## 5. Conclusion

Sepsis is typified by a dysregulated immune response to infection that can lead to organ damage, failure, and death. Sepsis has a significant mortality rate, and there has been a great deal of research into drug development, especially for adjuvant therapy. However, the majority of candidate drugs have not been found to be efficacious against sepsis [92].

Chinese herbal medicine has long been used for treating sepsis in China and has been found useful recently for treating COVID-19 [93]. There have been numerous investigations into the pharmacological actions of TCM, and recent reports have demonstrated the efficacy of ginsenosides for both preventing and treating inflammatory diseases through their modulation of inflammatory pathways. The mechanisms through which ginsenosides act appear to be through activating NLRP3, elevating GR protein levels, enhancing GC action, and blocking NF-κB and MAPK signaling. We think the last item may be the main control method. Ginsenosides counteract inflammatory factor release, including the secretion of TNF-α, IL-1β, and IL-6, through inhibiting MAPKs, such as p38, JNK, and ERK1/2, and thus blocking MAPK and NF-κB signaling, mitigating organ damage resulting from sepsis. In conclusion, ginsenosides and their metabolites or derivatives may have significant potential for preventing and treating sepsis and other forms of inflammation, thus providing new insights and directions for clinical therapy.

## Declaration of competing interest

The authors declare that they have no competing interests.

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