Journal of Ginseng Research 47 (2023) 1–8

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: https://www.sciencedirect.com/journal/journal-of-ginseng-research

Short Review

Roles of ginsenosides in sepsis

Tao Yu [a], Yidi Tang [a], Fenglan Zhang [b, **], Leiming Zhang [a, *]

[a] Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, School of Pharmacy, Yantai University, Yantai, China
[b] Yantai Yuhuangding Hospital, The Affiliated Hospital of Qingdao University, Yantai, China

ARTICLE INFO

Article history:
Received 25 February 2022
Received in revised form
20 April 2022
Accepted 2 May 2022
Available online 7 May 2022

Keywords:
Ginsenosides
Sepsis
COVID-19
NF-κB

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].

* Corresponding author. Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, School of Pharmacy, Yantai University, Yantai, 264005, China.
** Corresponding author.
E-mail addresses: zhangfenglan21st@126.com (F. Zhang), zhangleiming2009@126.com (L. Zhang).

https://doi.org/10.1016/j.jgr.2022.05.004

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

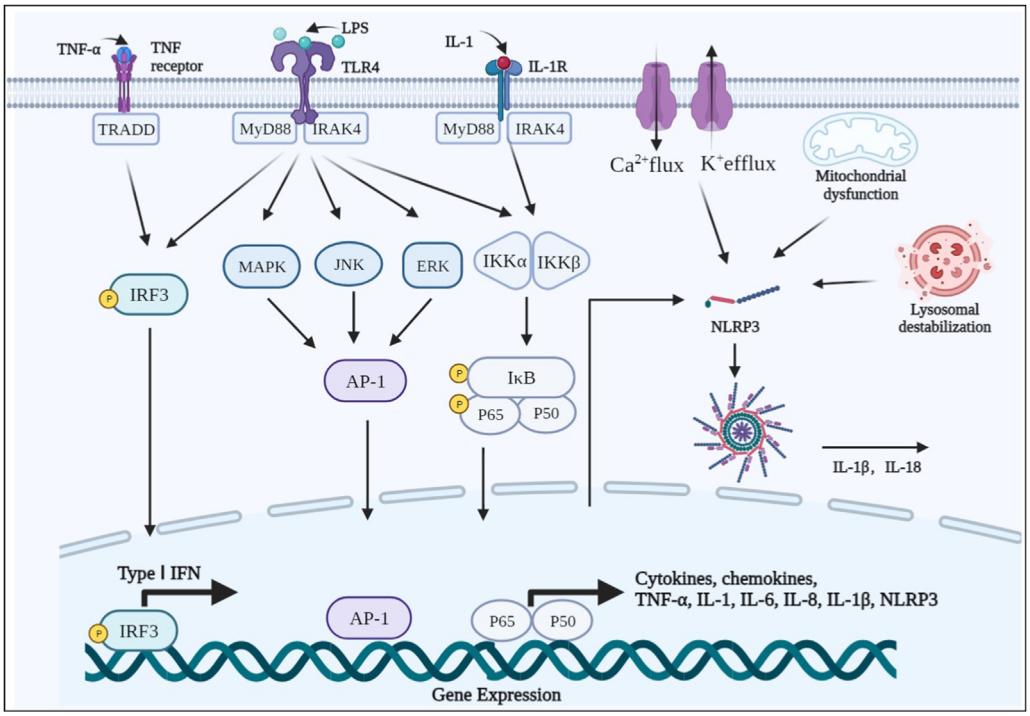

Fig. 1. Overview of the pathogenesis of acute inflammation in sepsis.
The binding of PAMPs, including peptidoglycans, flagellin, and LPS, to TLRs activates signaling pathways leading to the recruitment of IRAK4 and MyD88, resulting in IRF3 activation and IFN-I release. Activated TLRs act through MAPK, 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,

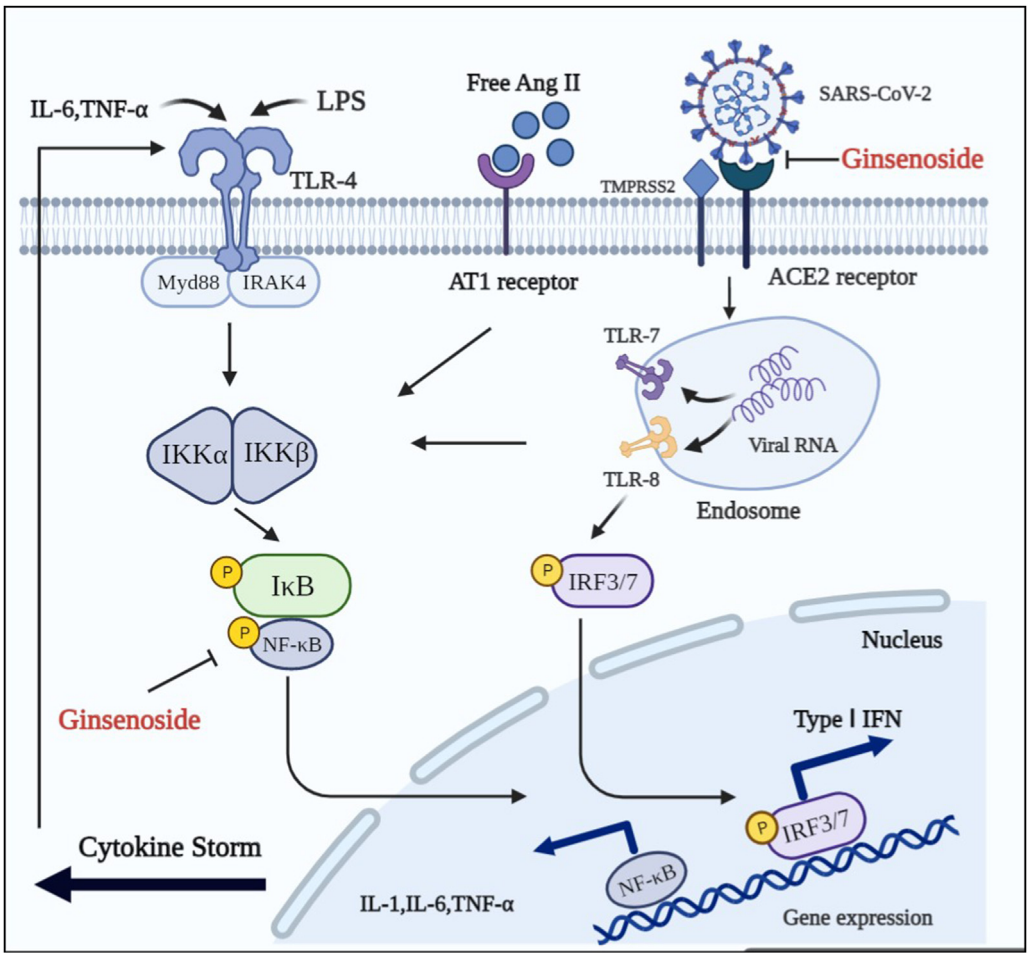

Fig. 2. Potential actions of ginsenosides in COVID-19 treatment
The proposed treatment targets NF-κB-mediated signaling that produces the cytokine storm. SARS-CoV-2 interacts with the angiotensin-converting enzyme 2 (ACE2) receptor and undergoes TMPRSS2-mediated endocytosis. The Toll-like receptors TLR7 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.

Acknowledgements

This work was supported by The National Natural Science Foundation of China (grant no. 81973547).

References

[1] Shankar HM, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M. Sepsis Definitions task F. Developing a new definition and assessing new clinical criteria for septic shock: for the third international Consensus Definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:775–87.
[2] Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392:75–87.
[3] Levi M, Schultz M, van der Poll T. Sepsis and thrombosis. Semin Thromb Hemost 2013;39:559–66.
[4] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200–11.
[5] Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014;312:90–2.
[6] Xie J, Wang H, Kang Y, Zhou L, Liu Z, Qin B, Ma X, Cao X, Chen D, Lu W, et al. The epidemiology of sepsis in Chinese ICUs: a national cross-sectional survey. Crit Care Med 2020;48:e209–18.
[7] Poston JT, Koyner JL. Sepsis associated acute kidney injury. BMJ 2019;364:k4891.
[8] Strnad P, Tacke F, Koch A, Trautwein C. Liver - guardian, modifier and target of sepsis. Nat Rev Gastroenterol Hepatol 2017;14:55–66.
[9] Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, Su X, Cao B. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 2020;395:1517–20.
[10] Im DS. Pro-resolving effect of ginsenosides as an anti-inflammatory mechanism of Panax ginseng. Biomolecules 2020;10.
[11] Tian M, Li LN, Zheng RR, Yang L, Wang ZT. Advances on hormone-like activity of Panax ginseng and ginsenosides. Chin J Nat Med 2020;18:526–35.

[12] Yi YS. New mechanisms of ginseng saponin-mediated anti-inflammatory action via targeting canonical inflammasome signaling pathways. J Ethnopharmacol 2021;278:114292.
[13] Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. Int J Mol Sci 2019;20.
[14] Bhan C, Dipankar P, Chakraborty P, Sarangi PP. Role of cellular events in the pathophysiology of sepsis. Inflamm Res 2016;65:853–68.
[15] Raymond SL, Holden DC, Mira JC, Stortz JA, Loftus TJ, Mohr AM, Moldawer LL, Moore FA, Larson SD, Efron PA. Microbial recognition and danger signals in sepsis and trauma. Biochim Biophys Acta (BBA) - Mol Basis Dis 2017;1863:2564–73.
[16] Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 2010;11:373–84.
[17] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity 2011;34:637–50.
[18] Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet 2005;365:63–78.
[19] Schroder K, Tschopp J. The inflammasomes. Cell 2010;140:821–32.
[20] Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol 2019;19:477–89.
[21] Munoz-Planillo R, Kuffa P, Martinez-Colon G, Smith BL, Rajendiran TM, Nunez G. K(+) efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity 2013;38:1142–53.
[22] Murakami T, Ockinger J, Yu J, Byles V, McColl A, Hofer AM, Horng T. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proc Natl Acad Sci U S A 2012;109:11282–7.
[23] Qiu Z, He Y, Ming H, Lei S, Leng Y, Xia ZY. Lipopolysaccharide (LPS) aggravates high glucose- and hypoxia/reoxygenation-induced injury through activating ROS-dependent NLRP3 inflammasome-mediated pyroptosis in H9C2 cardiomyocytes. J Diabetes Res 2019;2019:8151836.
[24] van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol 2017;17:407–20.
[25] Hagar JA, Powell DA, Aachoui Y, Ernst RK, Miao EA. Cytoplasmic LPS activates caspase-11: implications in TLR4-independent endotoxic shock. Science 2013;341:1250–3.
[26] Deng M, Tang Y, Li W, Wang X, Zhang R, Zhang X, Zhao X, Liu J, Tang C, Liu Z, et al. The endotoxin delivery protein HMGB1 mediates caspase-11-dependent lethality in sepsis. Immunity 2018;49:740–753 e7.
[27] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, Li W, Tong Q, Yi J, Zhao L, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020;55:102763.
[28] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[29] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77.
[30] Opal SM. The evolution of the understanding of sepsis, infection, and the host response: a brief history. Crit Care Clin 2009;25:637–63 [vii].
[31] Eisen DP. Manifold beneficial effects of acetyl salicylic acid and nonsteroidal anti-inflammatory drugs on sepsis. Intensive Care Med 2012;38:1249–57.
[32] Vandewalle J, Libert C. Glucocorticoids in sepsis: to Be or not to Be. Front Immunol 2020;11:1318.
[33] Heming N, Lamothe L, Ambrosi X, Annane D. Emerging drugs for the treatment of sepsis. Expet Opin Emerg Drugs 2016;21:27–37.
[34] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637.
[35] Marik PE. The role of glucocorticoids as adjunctive treatment for sepsis in the modern era. Lancet Respir Med 2018;6:793–800.
[36] Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809–18.
[37] Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797–808.
[38] Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. Trends Pharmacol Sci 2013;34:518–30.
[39] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. N Engl J Med 2005;353:1711–23.
[40] Lasa M, Abraham SM, Boucheron C, Saklatvala J, Clark AR. Dexamethasone causes sustained expression of mitogen-activated protein kinase (MAPK) phosphatase 1 and phosphatase-mediated inhibition of MAPK p38. Mol Cell Biol 2002;22:7802–11.
[41] Dendoncker K, Libert C. Glucocorticoid resistance as a major drive in sepsis pathology. Cytokine Growth Factor Rev 2017;35:85–96.
[42] Wilkinson L, Verhoog NJD, Louw A. Disease- and treatment-associated acquired glucocorticoid resistance. Endocr Connect 2018;7:R328–49.
[43] Shibata S, Fujita M, Itokawa H, Tanaka O, Ishii T. Studies on the constituents of Japanese and Chinese crude drugs. Xi. Panaxadiol, a sapogenin of ginseng roots. Chem Pharm Bull (Tokyo) 1963;11:759–61.
[44] Yuan Q, Jiang YW, Ma TT, Fang QH, Pan L. Attenuating effect of Ginsenoside Rb1 on LPS-induced lung injury in rats. J Inflamm 2014;11:40.
[45] Yu S, Zhou X, Li F, Xu C, Zheng F, Li J, Zhao H, Dai Y, Liu S, Feng Y. Microbial transformation of ginsenoside Rb1, Re and Rg1 and its contribution to the improved anti-inflammatory activity of ginseng. Sci Rep 2017;7:138.
[46] Joh EH, Lee IA, Jung IH, Kim DH. Ginsenoside Rb1 and its metabolite compound K inhibit IRAK-1 activation–the key step of inflammation. Biochem Pharmacol 2011;82:278–86.
[47] Shaukat A, Guo YF, Jiang K, Zhao G, Wu H, Zhang T, Yang Y, Guo S, Yang C, Zahoor A, et al. Ginsenoside Rb1 ameliorates Staphylococcus aureus-induced Acute Lung Injury through attenuating NF-kappaB and MAPK activation. Microb Pathog 2019;132:302–12.
[48] Wu LL, Jia BH, Sun J, Chen JX, Liu ZY, Liu Y. Protective effects of ginsenoside Rb1 on septic rats and its mechanism. Biomed Environ Sci 2014;27:300–3.
[49] Hua F, Shi L, Zhou P. Phytochemicals as potential IKK-beta inhibitor for the treatment of cardiovascular diseases in plant preservation: terpenoids, alkaloids, and quinones. Inflammopharmacology 2020;28:83–93.
[50] Lee IA, Hyam SR, Jang SE, Han MJ, Kim DH. Ginsenoside Re ameliorates inflammation by inhibiting the binding of lipopolysaccharide to TLR4 on macrophages. J Agric Food Chem 2012;60:9595–602.
[51] Quan HY, Jin XY, Cui EJ, Zhang Q. Lipopolysaccharide-induced inflammation is inhibited by ginsenoside Re through NF-kappa B signaling in RAW264.7 cells and primary rat hepatocytes. Lat Am J Pharm 2019;38:1969–78.
[52] Chen RC, Wang J, Yang L, Sun GB, Sun XB. Protective effects of ginsenoside Re on lipopolysaccharide-induced cardiac dysfunction in mice. Food Funct 2016;7:2278–87.
[53] Lee JH, Min DS, Lee CW, Song KH, Kim YS, Kim HP. Ginsenosides from Korean Red Ginseng ameliorate lung inflammatory responses: inhibition of the MAPKs/NF-kappaB/c-Fos pathways. J Ginseng Res 2018;42:476–84.
[54] Ryu S-J, Choi J, Lee J-S, Choi H-S, Yoon K-Y, Hwang J-H, Kim K, Lee B-Y. Compound K inhibits the lipopolysaccharide-induced inflammatory responses in raw 264.7 cell line and zebrafish. Appl Sci 2018;8.
[55] Liu Y, Perumalsamy H, Kang CH, Kim SH, Hwang JS, Koh SC, Yi TH, Kim YJ. Intracellular synthesis of gold nanoparticles by Gluconacetobacter liquefaciens for delivery of peptide CopA3 and ginsenoside and anti-inflammatory effect on lipopolysaccharide-activated macrophages. Artif Cell Nanomed Biotechnol 2020;48:777–88.
[56] Yang CS, Ko SR, Cho BG, Shin DM, Yuk JM, Li S, Kim JM, Evans RM, Jung JS, Song DK, et al. The ginsenoside metabolite compound K, a novel agonist of glucocorticoid receptor, induces tolerance to endotoxin-induced lethal shock. J Cell Mol Med 2008;12:1739–53.
[57] Nguyen TLL, Huynh DTN, Jin Y, Jeon H, Heo KS. Protective effects of ginsenoside-Rg2 and -Rh1 on liver function through inhibiting TAK1 and STAT3-mediated inflammatory activity and Nrf2/ARE-mediated antioxidant signaling pathway. Arch Pharm Res (Seoul) 2021;44:241–52.
[58] Park EK, Choo MK, Han MJ, Kim DH. Ginsenoside Rh1 possesses antiallergic and anti-inflammatory activities. Int Arch Allergy Immunol 2004;133:113–20.
[59] Jung JS, Kim DH, Kim HS. Ginsenoside Rh1 suppresses inducible nitric oxide synthase gene expression in IFN-gamma-stimulated microglia via modulation of JAK/STAT and ERK signaling pathways. Biochem Biophys Res Commun 2010;397:323–8.
[60] Kim J, Ahn H, Han BC, Lee SH, Cho YW, Kim CH, Hong EJ, An BS, Jeung EB, Lee GS. Korean red ginseng extracts inhibit NLRP3 and AIM2 inflammasome activation. Immunol Lett 2014;158:143–50.
[61] Li J, Du J, Liu D, Cheng B, Fang F, Weng L, Wang C, Ling C. Ginsenoside Rh1 potentiates dexamethasone's anti-inflammatory effects for chronic inflammatory disease by reversing dexamethasone-induced resistance. Arthritis Res Ther 2014;16:R106.
[62] Lee W, Cho SH, Kim JE, Lee C, Lee JH, Baek MC, Song GY, Bae JS. Suppressive effects of ginsenoside Rh1 on HMGB1-mediated septic responses. Am J Chin Med 2019;47:119–33.
[63] Hsieh YH, Deng JS, Chang YS, Huang GJ. Ginsenoside Rh2 ameliorates lipopolysaccharide-induced acute lung injury by regulating the TLR4/PI3K/Akt/mTOR, raf-1/MEK/ERK, and keap1/nrf2/HO-1 signaling pathways in mice. Nutrients 2018;10.
[64] Baatar D, Siddiqi MZ, Im WT, Ul Khaliq N, Hwang SG. Anti-inflammatory effect of ginsenoside Rh2-mix on lipopolysaccharide-stimulated RAW 264.7 murine macrophage cells. J Med Food 2018;21:951–60.
[65] Fu BD, Bi WY, He CL, Zhu W, Shen HQ, Yi PF, Wang L, Wang DC, Wei XB. Sulfated derivatives of 20(S)-ginsenoside Rh2 and their inhibitory effects on LPS-induced inflammatory cytokines and mediators. Fitoterapia 2013;84:303–7.
[66] Bi WY, Fu BD, Shen HQ, Wei Q, Zhang C, Song Z, Qin QQ, Li HP, Lv S, Wu SC, et al. Sulfated derivative of 20(S)-ginsenoside Rh2 inhibits inflammatory cytokines through MAPKs and NF-kappa B pathways in LPS-induced RAW264.7 macrophages. Inflammation 2012;35:1659–68.
[67] Zou Y, Tao T, Tian Y, Zhu J, Cao L, Deng X, Li J. Ginsenoside Rg1 improves survival in a murine model of polymicrobial sepsis by suppressing the inflammatory response and apoptosis of lymphocytes. J Surg Res 2013;183:760–6.
[68] Ning C, Gao X, Wang C, Huo X, Liu Z, Sun H, Yang X, Sun P, Ma X, Meng Q, et al. Protective effects of ginsenoside Rg1 against lipopolysaccharide/d-galactosamine-induced acute liver injury in mice through inhibiting toll-like receptor 4 signaling pathway. Int Immunopharm 2018;61:266–76.

[69] Wang QL, Yang L, Peng Y, Gao M, Yang MS, Xing W, Xiao XZ. Ginsenoside Rg1 regulates SIRT1 to ameliorate sepsis-induced lung inflammation and injury via inhibiting endoplasmic reticulum stress and inflammation. Mediat Inflamm 2019;2019:6453296.
[70] Luo M, Yan D, Sun Q, Tao J, Xu L, Sun H, Zhao H. Ginsenoside Rg1 attenuates cardiomyocyte apoptosis and inflammation via the TLR4/NF-kB/NLRP3 pathway. J Cell Biochem 2020;121:2994–3004.
[71] Song Y, Zhao F, Zhang L, Du Y, Wang T, Fu F. Ginsenoside Rg1 exerts synergistic anti-inflammatory effects with low doses of glucocorticoids in vitro. Fitoterapia 2013;91:173–9.
[72] Du J, Cheng B, Zhu X, Ling C. Ginsenoside Rg1, a novel glucocorticoid receptor agonist of plant origin, maintains glucocorticoid efficacy with reduced side effects. J Immunol 2011;187:942–50.
[73] Kim TW, Joh EH, Kim B, Kim DH. Ginsenoside Rg5 ameliorates lung inflammation in mice by inhibiting the binding of LPS to toll-like receptor-4 on macrophages. Int Immunopharm 2012;12:110–6.
[74] Kim JE, Lee W, Yang S, Cho SH, Baek MC, Song GY, Bae JS. Suppressive effects of rare ginsenosides, Rk1 and Rg5, on HMGB1-mediated septic responses. Food Chem Toxicol 2019;124:45–53.
[75] Shin YM, Jung HJ, Choi WY, Lim CJ. Antioxidative, anti-inflammatory, and matrix metalloproteinase inhibitory activities of 20(S)-ginsenoside Rg3 in cultured mammalian cell lines. Mol Biol Rep 2013;40:269–79.
[76] Yoon SJ, Park JY, Choi S, Lee JB, Jung H, Kim TD, Yoon SR, Choi I, Shim S, Park YJ. Ginsenoside Rg3 regulates S-nitrosylation of the NLRP3 inflammasome via suppression of iNOS. Biochem Biophys Res Commun 2015;463:1184–9.
[77] Shi Y, Wang H, Zheng M, Xu W, Yang Y, Shi F. Ginsenoside Rg3 suppresses the NLRP3 inflammasome activation through inhibition of its assembly. Faseb J 2020;34:208–21.
[78] Xin C, Kim J, Quan H, Yin M, Jeong S, Choi JI, Jang EA, Lee CH, Kim DH, Bae HB. Ginsenoside Rg3 promotes Fc gamma receptor-mediated phagocytosis of bacteria by macrophages via an extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent mechanism. Int Immunopharm 2019;77:105945.
[79] Lee B, Sur B, Park J, Kim SH, Kwon S, Yeom M, Shim I, Lee H, Hahm DH. Ginsenoside rg3 alleviates lipopolysaccharide-induced learning and memory impairments by anti-inflammatory activity in rats. Biomol Ther (Seoul) 2013;21:381–90.
[80] Xing W, Yang L, Peng Y, Wang Q, Gao M, Yang M, Xiao X. Ginsenoside Rg3 attenuates sepsis-induced injury and mitochondrial dysfunction in liver via AMPK-mediated autophagy flux. Biosci Rep 2017;37.
[81] Yang J, Li S, Wang L, Du F, Zhou X, Song Q, Zhao J, Fang R. Ginsenoside Rg3 attenuates lipopolysaccharide-induced acute lung injury via MerTK-dependent activation of the PI3K/AKT/mTOR pathway. Front Pharmacol 2018;9:850.
[82] Beltran-Garcia J, Osca-Verdegal R, Pallardo FV, Ferreres J, Rodriguez M, Mulet S, Sanchis-Gomar F, Carbonell N, Garcia-Gimenez JL. Oxidative stress and inflammation in COVID-19-associated sepsis: the potential role of anti-oxidant therapy in avoiding disease progression. Antioxidants 2020;9.
[83] Zhang D, Hamdoun S, Chen R, Yang L, Ip CK, Qu Y, Li R, Jiang H, Yang Z, Chung SK, et al. Identification of natural compounds as SARS-CoV-2 entry inhibitors by molecular docking-based virtual screening with bio-layer interferometry. Pharmacol Res 2021;172:105820.
[84] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Hlh Across Speciality Collaboration Uk. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
[85] Park HH, Kim HN, Kim H, Yoo Y, Shin H, Choi EY, Bae JS, Lee W. Acetylated K676 TGFBIp as a severity diagnostic blood biomarker for SARS-CoV-2 pneumonia. Sci Adv 2020;6.
[86] 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.
[87] Xiao Q, Zhang S, Yang C, Du R, Zhao J, Li J, Xu Y, Qin Y, Gao Y, Huang W. Ginsenoside Rg1 ameliorates palmitic acid-induced hepatic steatosis and inflammation in HepG2 cells via the AMPK/NF-kappaB pathway. Internet J Endocrinol 2019;2019:7514802.
[88] Brasier AR. The nuclear factor-kappaB-interleukin-6 signalling pathway mediating vascular inflammation. Cardiovasc Res 2010;86:211–8.
[89] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
[90] Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity 2020;52:731–3.
[91] Divani AA, Andalib S, Di Napoli M, Lattanzi S, Hussain MS, Biller J, McCullough LD, Azarpazhooh MR, Seletska A, Mayer SA, et al. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. J Stroke Cerebrovasc Dis 2020;29:104941.
[92] Vignon P, Laterre PF, Daix T, Francois B. New agents in development for sepsis: any reason for hope? Drugs 2020;80:1751–61.
[93] Ren JL, Zhang AH, Wang XJ. Corrigendum to "traditional Chinese medicine for COVID-19 treatment" [pharmacol. Res. 155 (2020) 104743]. Pharmacol Res 2020;155:104768.
[94] Yu XQ, Robbie GJ, Wu Y, Esser MT, Jensen K, Schwartz HI, Bellamy T, Hernandez-Illas M, Jafri HS. Safety, tolerability, and pharmacokinetics of MEDI4893, an investigational, extended-half-life, anti-Staphylococcus aureus alpha-toxin human monoclonal antibody, in healthy adults. Antimicrob Agents Chemother 2017;61.
[95] Ali SO, Yu XQ, Robbie GJ, Wu Y, Shoemaker K, Yu L, DiGiandomenico A, Keller AE, Anude C, Hernandez-Illas M, et al. Phase 1 study of MEDI3902, an investigational anti-Pseudomonas aeruginosa PcrV and Psl bispecific human monoclonal antibody, in healthy adults. Clin Microbiol Infect 2019;25:629 e1–e6.
[96] Vincent JL, Francois B, Zabolotskikh I, Daga MK, Lascarrou JB, Kirov MY, Pettila V, Wittebole X, Meziani F, Mercier E, et al. Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial. JAMA 2019;321:1993–2002.
[97] Geven C, Blet A, Kox M, Hartmann O, Scigalla P, Zimmermann J, Marx G, Laterre PF, Mebazaa A, Pickkers P. A double-blind, placebo-controlled, randomised, multicentre, proof-of-concept and dose-finding phase II clinical trial to investigate the safety, tolerability and efficacy of adrecizumab in patients with septic shock and elevated adrenomedullin concentration (AdrenOSS-2). BMJ Open 2019;9:e024475.
[98] Leentjens J, Kox M, Koch RM, Preijers F, Joosten LA, van der Hoeven JG, Netea MG, Pickkers P. Reversal of immunoparalysis in humans in vivo: a double-blind, placebo-controlled, randomized pilot study. Am J Respir Crit Care Med 2012;186:838–45.
[99] François B, Wittebole X, Ferrer R, Mira J-P, Dugernier T, Gibot S, Derive M, Olivier A, Cuvier V, Witte S, et al. Nangibotide in patients with septic shock: a Phase 2a randomized controlled clinical trial. Intensive Care Med 2020;46:1425–37.
[100] Francois B, Jeannet R, Daix T, Walton AH, Shotwell MS, Unsinger J, Monneret G, Rimmele T, Blood T, Morre M, et al. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI Insight 2018;3.