



# Resveratrol: Potential Application in Sepsis

Jiajia Li<sup>†</sup>, Xiaoting Zeng<sup>†</sup>, Fuxun Yang, Lan Wang, Xiaoxiu Luo, Rongan Liu, Fan Zeng, Sen Lu, Xiaobo Huang\*, Yu Lei\* and Yunping Lan\*

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

Sepsis is a life-threatening organ dysfunction syndrome caused by host response disorders due to infection or infectious factors and is a common complication of patients with clinical trauma, burns, and infection. Resveratrol is a natural polyphenol compound that is a SIRT-1 activator with anti-inflammatory, antiviral, antibacterial, antifungal inhibitory abilities as well as cardiovascular and anti-tumor protective effects. In recent years, some scholars have applied resveratrol in animal models of sepsis and found that it has an organ protective effect and can improve the survival time and reduce the mortality of animals with sepsis. In this study, Medline (Pubmed), embase, and other databases were searched to retrieve literature published in 2021 using the keywords “resveratrol” and “sepsis,” and then the potential of resveratrol for the treatment of sepsis was reviewed and prospected to provide some basis for future clinical research.

**Keywords:** sepsis, resveratrol, organ protection, antioxidation, SIRT-1, animal model

## INTRODUCTION

Sepsis develops following a dysregulated host immune response in patients with clinical trauma, burns, and infection leading to organ dysfunction. Progression to septic shock leads to multiple organ dysfunction syndromes, which is the primary cause of death in critically ill clinical patients, with a mortality rate reaching up to 30%–70% (Singer et al., 2016). The pathogenic factors and mechanisms contributing to sepsis are multifactorial and complex, including epigenetic and transcriptional regulation disorders, neuroendocrine-immune network disorders, coagulation abnormalities, tissue and organ damage, as well as inflammatory metabolic damage and microbial toxin effects (Singer et al., 2016; van der Poll et al., 2017; Cecconi et al., 2018). Therefore, it has been challenging to identify an effective agent for the prevention and treatment of sepsis that can address all of these factors while having a good safety profile.

Resveratrol (C<sub>14</sub>H<sub>12</sub>O<sub>3</sub>, molecular weight 228.25) is a polyphenol antitoxin produced by plants in response to exogenous stimuli, such as ultraviolet light, mechanical damage, or fungal infection (Sanders et al., 2000). Resveratrol is widely distributed in plants' roots, stems, leaves, and fruits and is well known for its potent antioxidant activity. Its name is derived from the roots of white hellebore, where it was first identified in 1940 (Shakibaei et al., 2009) and has since been widely identified in grapes, knotweed, peanuts, mulberries, blueberries, spruce, and other plant roots, leaves, and fruits (García-Pérez et al., 2012). Polyphenols inhibit NF-κB activation and downregulate nitric oxide synthase, adhesion molecules, and tumor necrosis factor-α. The expression of polyphenols and the enhancement of endogenous antioxidant capacity may also contribute to the effectiveness of polyphenols, which can effectively improve sepsis-related organ damage (Shapiro et al., 2009). Resveratrol is an effective Sirtuin-1 (SIRT-1) (Arunachalam et al., 2010) activator with anti-inflammatory (Zimmermann-Franco et al., 2018), antiviral (Campagna and Rivas 2010),

## OPEN ACCESS

### Edited by:

Namrita Lall,  
University of Pretoria, South Africa

### Reviewed by:

Milad Ashrafzadeh,  
Sabanci University, Turkey

### \*Correspondence:

Xiaobo Huang  
drhuangxb@163.com  
Yu Lei  
274410207@qq.com  
Yunping Lan  
lanyunping929@163.com

<sup>†</sup>These authors have contributed equally to this work

### Specialty section:

This article was submitted to  
Ethnopharmacology,  
a section of the journal  
Frontiers in Pharmacology

**Received:** 24 November 2021

**Accepted:** 21 January 2022

**Published:** 09 February 2022

### Citation:

Li J, Zeng X, Yang F, Wang L, Luo X,  
Liu R, Zeng F, Lu S, Huang X, Lei Y and  
Lan Y (2022) Resveratrol: Potential  
Application in Sepsis.  
Front. Pharmacol. 13:821358.  
doi: 10.3389/fphar.2022.821358

**TABLE 1 |** Application of resveratrol in different organs of sepsis models.

Organ or system	Dosage	Pathway or mechanism	References NO.
Lung	40 mg/kg	↑VEGF-B; ↓ TNF- $\alpha$ , IL-6, IL-1 $\beta$	Yang et al. (2018)
MH-S cell	10 $\mu$ M	↑VEGF-B siRNA; ↓ NF- $\kappa$ B phosphorylation, ERK1/2 and p38; ↓ Bax ↑ Bcl-2; ↓ LC3-II/Iratio; ↓ C5aR; ↑C5L2	Yang et al. (2018)
Lung	0.3 mg/kg	↓MDA and H2O2; ↑GSH/GSSG ratio, T-AOC, CAT and SOD activity; ↓iNOS and NO; ↓Peroxynitrite	Zhang et al. (2014)
Lung	30 mg/kg	↓PI3K/Nrf2/HO-1 pathway	Wang et al. (2018b)
Lung	60 mg/kg	↓JAK2/STAT3 pathway	Ji et al. (2016)
Lung/Kidney	30 mg/kg	↓MDA, ↑GSH; ↓Collagen content; ↓TNF- $\alpha$ and LDH activity	Kolgazi et al. (2006)
Heart	30 mg/kg	↑PI3K/AKT/mTOR pathway	Shang et al. (2019)
Heart	10 $\mu$ g	↓TNF- $\alpha$ , IL-1 $\beta$ , MIP-1 $\alpha$ , MCP; ↑Nrf2, ↑ gene HO-1 and GCLM expression	Hao et al. (2013)
Myocardial Cells	3 $\mu$ M	↓caspase 3 activation; ↓ROS; ↑ Nrf2 Activation	Hao et al. (2013)
Heart	20 mg/kg	↓MDA; ↑SOD and POD; ↓CAT; ↓NO	Sebai et al. (2011)
Heart	20 mg/kg	↑SERCA2a activation	Bai et al. (2016)
Heart	30 or 60 mg/kg	↑PGC-1 mRNA, Protein expression and transcriptional activity	Smeding et al. (2012)
Heart	60 mg/kg	↓TNF- $\alpha$ and MPO; ↑ Sirt1 and Bcl-2 expression; ↓ Ac-FoxO1 and Bax expression	An et al. (2016)
Heart	60 mg/kg	Activation of Sirt1 signal, ↓ neutrophil aggregation, TNF- $\alpha$ expression and myocardial cell apoptosis	An et al. (2016)
Kidney	10 mg/kg	↓NO; Improve microcirculation	Holthoff et al. (2012)
Kidney	15 mg/kg	↓ TLR4-NF- $\kappa$ B pathway	Chen et al. (2015)
Kidney	15 ml/kg	↓NF- $\kappa$ B Activation; ↓Er stress	Luo et al. (2020)
Kidney	30 mg/kg	↓IRE1-NF- $\kappa$ B pathway	Nian Wang et al. (2017)
Kidney	50 mg/kg	Recovery of SIRT1/3 activity, ↓ acetylation of SOD2, ↑GSH, GSH/GSSG ratio and CAT activity; ↑ATP content, ↓ mPTP opening	Xu et al. (2016)
Kidney	3, 10, 30, 100 mg/kg	↑renal capillary perfusion, RBC velocity, and blood flow	Holthoff, et al. (2011)
Kidney	100 mg/kg	↓TNF $\alpha$ , IL-1 $\beta$ , IL-6 and McP-1; ↓Renal vascular permeability; ↑IL10; ↓Bcl-2 and Bcl-XL	Chen, et al. (2015)
BMDM	10, 20, 50, 100 $\mu$ mol	↓TLR4-NF- $\kappa$ B pathway	Chen, et al. (2015)
BV2	15 or 30 $\mu$ M	↓NLRP3, caspase - 1 and IL - 1 $\beta$	Sui et al. (2016)
Liver	60 mg/kg/d	↓HMGB1 Cytoplasmic translocation	Xu et al. (2014)
Brain	10 and 30 mg/kg	↓apoptosis; ↓ IBA-1; ↓NLRP3 and IL-1 $\beta$	Sui et al. (2016)
Brain	30 $\mu$ M	↓ NLRP3 and IL-1 $\beta$ cracking	Sui et al. (2016)
Brain	8 mg/kg/d	↓MMP-9protein, ↓Occludin and Claudin-5 degradation	Liu et al. (2020)
Circulation	30 mg/kg	↓Total blood viscosity and local blood flow	Wang et al. (2018a)
Circulation	30 mg/kg	↑ RhoA-ROCK-MLCPpathway	Xu-Qing Wang et al. (2017)
Circulation	5 mg/kg and 10 mg/kg	↓Rac-1 and HIF-1 $\alpha$ ; ↑eNOS expression	Zhang et al. (2019)
Circulation	30 mg/kg	↓White cell/platelet adhesion, ↓ E - element/ICAM 1; ↑SIRT1; ↓E-selectin/ICAM-1	Xianfeng Wang et al. (2015)
Immune	1, 5, 10, 20, or 40 $\mu$ M	↓ TNF- $\alpha$ and IL-6, ↓MAPK and STAT1/STAT3; ↑SOCS1; ↓ miR-155 expression	Ma et al. (2017)
Immune	50 $\mu$ M	↓ TRAF6 expression and ubiquitination, ↓ TLR4-TRAF6; ↓ MAPK and Akt pathway	Jakus et al. (2013)
Immune	30, 50 $\mu$ M	↓ TRIF-TBK1-RIP1 pathway	Youn et al. (2005)
Immune	10–500 IM	↓ TNF- $\alpha$ , IL-1 $\beta$ , IL-6, MCP-1, MIP1 $\alpha$ 和HMGB-1; ↓ NF - $\kappa$ B activation, SphK activity and ERK1/2 phosphorylation	Sebai et al. (2010)
Immune	1 mg/kg	↓ PLD, SphK1, ERK1/2 and NF $\kappa$ B signaling molecules Activation	Wang et al. (2020)
Immune	100 mg/kg	↓ DNA damage of lymphocytes	Aydin et al. (2013)
Immune	50 or 300 $\mu$ M	↓ Ca2 +/CaMKK $\beta$ pathway, ↓ AMPK activation, ↓ IRAK-M and SHIP1	Quan et al. (2021)
Gastrointestinal Tract	100 mg/kg	↓ TNF $\alpha$ and IL-6; ↓ Ileum smooth muscle reaction	Gacar et al. (2012)
Adrenal Gland	0.3 mg/kg	↓ iNOS, NO, peroxynitrite; Left the MDA; ↑T-AOC, CAT and SOD activities	Duan et al. (2016)

antibacterial, and antifungal inhibitory properties (Lu et al., 2008). It also possesses cardiovascular and anti-tumor protective effects (Shang et al., 2019) (Ashrafzadeh et al., 2021).

In recent years, some scholars have applied resveratrol in animal models of sepsis. The application of resveratrol in endotoxemia rats can reduce the occurrence of oxidative damage by inhibiting erythrocyte lipid peroxidation and catalase (CAT) activity, reducing nitric oxide (NO) release, downregulating malondialdehyde (MDA) levels, and

maintaining iron homeostasis (Sebai et al., 2009). Resveratrol can induce increased activation of AMPK in macrophages stimulated by lipopolysaccharide (LPS) via the Ca<sup>2+</sup>/CaMKK $\beta$  pathway. This leads to protection against bacterial infections by increasing phagocytosis, regulating inflammatory status, and inhibiting the development of endotoxin tolerance by inhibiting the expression of IRAK-M and SHIP-1 induced by LPS (Quan et al., 2021). Recent studies have found that resveratrol also protects organ function during sepsis in

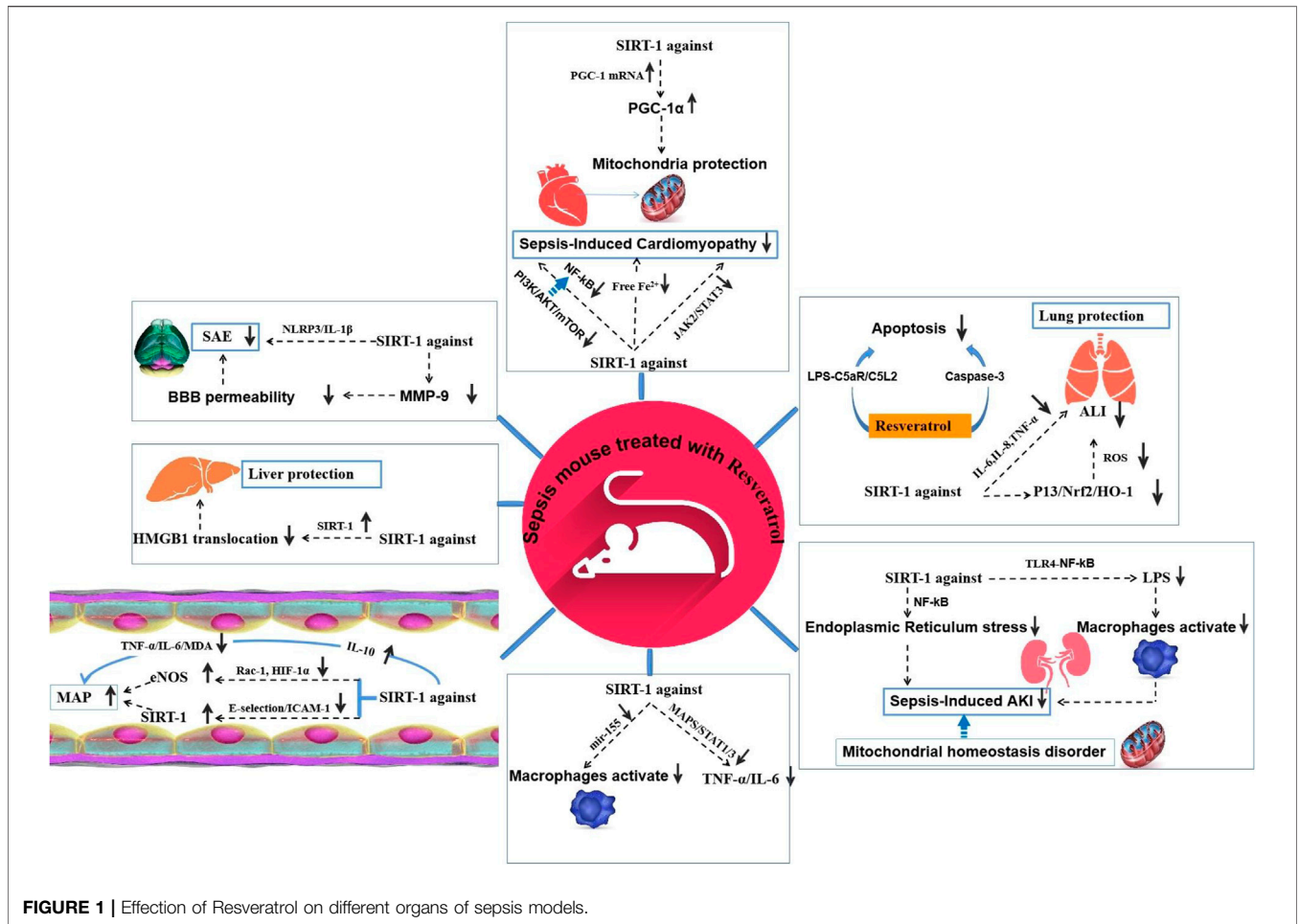


FIGURE 1 | Effect of Resveratrol on different organs of sepsis models.

various ways. This paper summarizes its organ protective effects and application potential in sepsis and offers direction for future research based on the results of various studies (Table 1).

## MATERIALS AND METHODS

Two authors searched the literature published in 2021 through MEDLINE (PubMed), EMBASE, and other databases. Using “resveratrol” and “sepsis” as keywords, they included the literature meeting the following criteria: patients with sepsis and animal models of sepsis were studied; studies were clinical trials or animal experiments of resveratrol intervention; and the primary endpoints were changes in organ function, circulatory status, and inflammatory response. Three authors conducted this study in three stages: analyzing the title followed by the abstract and, finally, reading the full text in detail. They were able to retrieve 77 articles from PubMed and 181 from EMBASE; 144 irrelevant articles were excluded by title, 41 were duplicate articles (114 in two databases), and four systematic reviews were excluded after reading the abstracts. One meeting abstract, three non-English studies, 17 non-sepsis studies, and 14 low-quality literature pieces were also excluded. Finally, 34 studies were

included after reading the full text. These included basic studies, including animal experiments and cell experiments, on the effects of resveratrol on the lung, heart, kidney, liver, brain, adrenal gland, gastrointestinal function, and circulatory and immune systems of sepsis models.

## EFFECTS OF RESVERATROL ON VARIOUS ORGANS/SYSTEMS IN SEPSIS MODELS

### Lung

The lung is the most readily injured organ in sepsis, and acute lung injury is one of the first manifestations of sepsis with the highest incidence among affected organs (Rubinfeld et al., 2005; Matthay et al., 2019). Yang et al. (2018) demonstrated that resveratrol treatment significantly reduced acute lung injury induced by cecal ligation and puncture (CLP) in mice (Figure 1). This protective effect could be attributed to the ability of resveratrol to modulate the autophagy and anti-apoptotic effects of C5aR and C5L2 induced by LPS. Moreover, resveratrol can reduce the expression levels of inflammatory factors associated with the response to infection, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-

1 $\beta$ , by inhibiting the vascular endothelial growth factor-B pathway. In addition, resveratrol pretreatment (Zhang et al., 2014) inhibited the expression of induced nitric oxide synthase (iNOS) and the production of NO caused by endotoxemia. It also significantly reduced the formation of peroxynitrite in lung tissues. These findings support the therapeutic potential of resveratrol in reducing acute lung injury caused by oxidative/nitrification processes.

Moreover, resveratrol downregulates inflammatory mediators (IL-8, RANTES, IL-1 $\alpha$ , IL-6, TNF- $\alpha$ , and CXCL10) and has specific inhibitory effects on acute lung injury caused by respiratory viruses. *In vitro* studies suggest that caspase-3 levels in infected cells treated with resveratrol reduce virus-induced apoptosis (Filardo et al., 2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can strongly induce the release of cytokines and chemokines resulting in cytopathy and organ dysfunction. Resveratrol inhibits excessive inflammation and oxidative responses in elderly COVID-19 patients by activating Nrf2 in aging vascular smooth muscle cells to reduce the production of mitochondrial reactive oxygen species (ROS) (Liao et al., 2021). Resveratrol may also play a positive role in sepsis-related injuries caused by viruses. In a rat model of sepsis, it was found that the use of resveratrol can reduce the levels of MDA and myeloperoxidase in lung and kidney tissues and increase the content of glutathione. This effect balances the oxidant-antioxidant state and reduces the oxidative damage of lung and kidney tissues (Kolgazi et al., 2006). At the same time, a previous study showed that timely administration of resveratrol after the occurrence of sepsis could reduce the degree of acute lung injury in septic rats by inhibiting inflammation, oxidative stress, and apoptosis via the inhibition of the PI3K/Nrf2/HO-1 signaling pathway (Wang et al., 2018b). These data further support the view that resveratrol plays an active role in the Nrf-2 signaling pathway (Farkhondeh et al., 2020).

## Heart

Sepsis-induced cardiomyopathy is a common complication of sepsis. Approximately 50% of sepsis patients will suffer from myocardial injury to varying degrees, and the mortality rate of sepsis patients with such complications is approximately 80% (Flierl et al., 2008). The pathogenesis of sepsis-induced cardiomyopathy is extremely complex and remains in an early exploration stage despite extensive efforts. Recent studies have shown that the occurrence of sepsis-induced cardiomyopathy is the result of a variety of factors including myocardial inhibition; mitochondrial dysfunction; oxidative stress; and imbalance of calcium regulation, apoptosis, and adrenoceptors (L'Heureux et al., 2020). Shang et al. used resveratrol as an intervention for septic myocarditis in a rat model, showing protection of the septic myocardium by activating the PI3K/AKT/mTOR signaling pathway and inhibiting the NF- $\kappa$ B signaling pathway and related inflammatory factors (Shang et al., 2019). In addition, Hao et al. (2013) revealed that resveratrol preconditioning can inhibit LPS-induced ROS production by activating the Nrf2 pathway in a rat myocardial injury model *in vivo* and in primary cultured human cardiomyocytes *in vitro*. At the same time, the use of resveratrol

in the CLP sepsis rat model decreased the sepsis-induced cardiomyocyte apoptosis and reduced the inflammatory cytokine TNF- $\alpha$  in serum and IL-1 $\beta$  in myocardial tissues. It also inhibited activation of the Janus activated kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT 3) pathway, thereby reducing myocardial damage (Ji et al., 2016).

Sebai et al. (2011) also found that resveratrol can antagonize LPS-induced lipid peroxidation, decrease the activity of superoxide dismutase (SOD), and reverse the increase in myocardial NO production induced by LPS. More importantly, resveratrol could reduce the LPS-induced decrease in myocardial free iron and reduce overall cardiotoxicity.

The systematic inflammatory cascade associated with sepsis can cause myocardial contractile dysfunction by impairing the calcium response (Shankar-Hari et al., 2016a; Shankar-Hari et al., 2016b). Resveratrol improved cardiac dysfunction in an LPS-induced endotoxemia mouse model. The mechanism for this protective effect was attributed to enhanced sarcoplasmic endoplasmic reticulum Ca<sup>2+</sup>-ATPase activity by promoting the oligomerization of phospholamban (Bai et al., 2016). Peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) is a coactivator of nuclear transcription that plays a key role in regulating the activity of many types of nuclear receptors. Among them, PGC-1 $\alpha$ , the first and most well-studied signaling pathway, is the transcriptional coactivator of mitochondrial-related genes and participates in regulating of mitochondrial biosynthesis and function. The PGC-1 $\alpha$  signaling pathway can promote the synthesis of myocardial mitochondria, induce energy production, maintain the contractile and diastolic function of the myocardium, and enhance the ability of cardiomyocytes to resist oxidative damage (Karunakaran et al., 2015). In another study (Smeding et al., 2012), resveratrol (30 mg/kg or 60 mg/kg) was subcutaneously injected into the neck of a CLP sepsis model, which caused an increase in PGC-1 mRNA and protein expression as well as transcriptional activity and further improved the mitochondrial integrity of the heart tissue compared with that of the control group as assessed with electron microscopy.

As one of the most extensively studied pathways of the cardiovascular system, the SIRT-1 pathway is highly sensitive to the cellular redox state and resists ROS through the deacetylation of various of cells, thus protecting and maintaining the vascular function of the heart (Nadtochiy et al., 2011a; Nadtochiy et al., 2011b; Vinciguerra et al., 2012; Hwang et al., 2013). Resveratrol effectively activates the SIRT-1 pathway as well. SIRT-1 activation improves mitochondrial function, increases ATP production in cells, and improves cellular metabolism (Price et al., 2012). Through the SIRT-1 pathway, resveratrol can exert a wide range of anti-inflammatory effects leading to beneficially therapeutic outcomes in inflammatory diseases (Dai et al., 2018). SIRT-1 can also control endothelial homeostasis and vascular function by regulating the expression of endothelial nitric oxide synthase (eNOS) activity, p53, and angiotensin II (Ang II) type 1 receptor (AT1R) (Kitada et al., 2016).

In the rat model of CLP-induced myocardial injury, intraperitoneal injection of resveratrol (An et al., 2016) was

able to reduce myocardial injury during sepsis by decreasing neutrophil accumulation, producing the myocardial cytokine TNF- $\alpha$ , activating the SIRT-1 pathway, reducing the production of myeloperoxidase, and suppressing cardiomyocyte apoptosis.

## Kidney

Overall, 36% of critically ill patients in the intensive care unit suffer from acute kidney injury (AKI) during hospitalization (Bagshaw et al., 2009). Among AKI patients without severe underlying diseases, the mortality rate can reach up to 10%–20% (Hoste et al., 2018). It has been reported that 40%–70% of AKI cases in the United States are caused by sepsis (Fani et al., 2018), and the mortality rate of septic AKI (SAKI) is significantly higher than that of AKI or sepsis alone (Bagshaw et al., 2009). The pathogenesis of SAKI has not yet been fully elucidated, although inflammation, oxidative stress, microvascular endothelial dysfunction, and renal tubular epithelial cell injury have all been proposed to play a role.

When LPSs enter the body, the LP-binding protein binds to CD14 and becomes an endotoxin monomer, which is transferred to the copolymer formed by TLR4 and MD2 adaptor protein, activating the TLR4 receptor to, in turn, activate the NF- $\kappa$ B pathway, ultimately increasing the production of pro-inflammatory factors, such as IL-6, and aggravating the inflammatory response of the kidney tissue. In the early stage of sepsis, renal microvascular disorders are related to the production of active nitrogen. As an effective polyphenol vasodilator, resveratrol protects renal tubular epithelial cells by improving renal microcirculation and eliminating the dual mechanism of active nitrogen species, thus reducing renal injury in sepsis (Holthoff et al., 2011). In addition, LPS-induced iron mobilization from the plasma to the kidney could be eliminated by resveratrol treatment. These results suggest that resveratrol has a strong antioxidant effect on LPS-induced nephrotoxicity, and its mode of action seems to be related to the iron shuttle protein (Holthoff et al., 2012).

Chen et al. also demonstrated that resveratrol can effectively regulate the activation of LPS-stimulated macrophages via the TLR4-NF- $\kappa$ B signaling pathway, thereby reducing the inflammatory response (Chen et al., 2015). In addition, Luo et al. (2020) showed that resveratrol could reduce renal injury in a septic rat model by inhibiting the activation of NF- $\kappa$ B and reducing endoplasmic reticulum stress. Subsequently, Nian Wang et al. (2017) found that resveratrol treatment immediately after successful establishment of the LPS-induced sepsis model could inhibit the phosphorylation of inositol demand enzyme 1 (IRE1) and NF- $\kappa$ B in the kidney. This conclusion was further supported with *in vitro* models suggesting that resveratrol can prevent septic AKI mainly by inhibiting renal inflammation triggered by the IRE1-NF- $\kappa$ B pathway. It was also found in another animal experiment that resveratrol can reduce LPS-induced cytokine production, decrease the concentrations of IL-1 $\beta$ , IL-6, MCP-1, and TNF- $\alpha$  in plasma and kidney, and decrease the renal tubular vacuole changes and pathological apoptosis (Chen et al., 2015).

In recent years, the role of mitochondrial dysfunction in SAKI pathogenesis has received increasing attention. Resveratrol is a chemical SIRT-1 activator that can effectively restore SIRT-1/3 activity, reduce the level of acetylated SOD2 (ac-SOD2), improve oxidative stress and mitochondrial function of renal tubular epithelial cells, and prolong survival time. Mice with renal injury and sepsis showed decreased SIRT-1/3 activity as well as increased ac-SOD2 levels, oxidative stress, and mitochondrial damage. All of these parameters improved following resveratrol treatment. This suggests that the protective effect of resveratrol on renal function may depend on SIRT1-mediated SOD2 deacetylation to maintain mitochondrial homeostasis (Xu et al., 2016).

## Liver

Sepsis-induced liver injury is often undetected and neglected in clinical settings despite this injury substantially increasing the risk of death from sepsis. Therefore, there is an urgent need to clarify the mechanism of sepsis-induced liver injury and to identify new therapeutic targets to improve the survival outcomes of these patients. In acute liver failure, high-mobility group protein-1 (HMGB1) translocation from the nucleus to the cytoplasm increases (Zhou et al., 2011) and inhibition of HMGB1 secretion alleviate systemic inflammatory response syndrome and sepsis-induced organ damage (Wang et al., 2008). Conversely, the release of HMGB1 from hepatocytes increases the risk of liver damage during sepsis. Therefore, inhibition of the translocation and release of HMGB1 can potentially prevent liver injury during sepsis and may provide a wider treatment window. Sepsis-induced serum transaminase activity and pro-inflammatory chemokine levels were decreased by resveratrol pretreatment, which also improved the liver histological parameters associated with the upregulation of SIRT-1. Knockout of SIRT-1 *in vitro* further confirmed that resveratrol increased the inhibition of SIRT-1-mediated HMGB1 translocation (Xu et al., 2014).

## Brain

Sepsis-associated encephalopathy (SAE) is characterized by brain dysfunction associated with sepsis, and its mechanisms include the production of inflammatory cytokines, microscopic brain injury, blood-brain barrier damage, changes in brain metabolism, changes in nerve transmission, and disruption of the brain microcirculation (Gofton and Young 2012). Microglia are highly activated in SAE, depending on injury to the nerve, humoral pathway, or blood-brain barrier (Gofton and Young 2012). In LPS-exposed astrocytes, resveratrol upregulates adenosine receptor expression and exerts anti-inflammatory effects by inhibiting NF $\kappa$ B and p38 mitogen-activated protein kinase (p38 MAPK) through the activation of Nrf-2/HO-1, SIRT-1, and PI3K/Akt pathways (Bobermin et al., 2019). In a study done by Sui et al. (2016), SAE was induced in mice by CLP; mice treated with resveratrol at 10 and 30 mg/kg demonstrated better spatial memory during water maze training compared to those in the control group. Moreover, resveratrol effectively inhibited the increase in NLRP3 expression and IL-1 $\beta$  cleavage in a dose-dependent manner. Subsequent *in vitro* experiments in the BV2 microglial cell line showed that resveratrol prevented

ATP-induced NLRP3 activation and IL-1 $\beta$  cleavage, which was reversed by treatment with the SIRT-1 inhibitor nicotinamide. These findings suggested that the protective effect of resveratrol on mice SAE is achieved by regulating the NLRP3/IL-1 $\beta$  pathway and that the increase in blood-brain barrier permeability during sepsis is a key link in the occurrence and development of SAE (Varatharaj and Galea 2017). Liu et al. injected 12-week-old male rats with 8 mg/kg resveratrol twice daily for 2 days, which inhibited the expression of matrix metalloproteinase-9 protein in cortical astrocytes, thus reducing the degradation of occludin and claudin-5 tight junction proteins to strengthen the blood-brain barrier, and finally reduced the degree of cognitive dysfunction caused by SAE (Liu et al., 2020).

## Circulation

Sepsis-related microcirculation failure is widely observed in clinical settings. It involves complex pathogenesis including the uncontrolled release of inflammatory mediators that contribute to sepsis itself. The injury of endothelial cells, instability of the macrocirculation, disturbance of blood coagulation, and activation of peroxide all lead to disturbance of the microcirculation (Ait-Oufella et al., 2015; Ratiani et al., 2015). In early stages of septic shock, the parasympathetic effect of LPS leads to blood flow redistribution and hemodilution and further reduces the local blood flow in the spleen and kidney. However, resveratrol treatment was shown to partially recover whole blood viscosity and local blood flow while also increasing the white blood cell content in the peripheral blood (Wang et al., 2018a). A meta-analysis of an animal model of sepsis with resveratrol intervention suggested that resveratrol can reduce the sepsis-induced inflammatory response by reducing TNF- $\alpha$ , MDA, and IL-6 levels; increasing IL-10 levels; and improving mean arterial pressure, thus improving the microcirculation (Zhou et al., 2019).

Hypovascular reactivity often occurs in the late shock stages during sepsis development. This is an important factor contributing to microcirculation disturbance and tissue hypoperfusion and further leads to multiple organ injury and dysfunction. Xu-Qing Wang et al. (2017) showed that resveratrol could maintain better mean arterial pressure in rats with LPS-induced sepsis. *In vitro* experiments revealed that resveratrol enhanced the vascular response of mice to LPS challenge through the RhoA-ROCK-MLCP signal pathway. Zhang et al. (2019) further showed that resveratrol dose-dependently inhibited the upregulation of eNOS expression by Rac-1 and HIF-1 $\alpha$ , improved hemodynamics, reduced the decrease of hepatic and renal blood flow, and enhanced the vasodilation response of septic shock rats. Similarly, resveratrol decreased leukocyte/platelet adhesion and E-selectin/ICAM-1 expression, and increased SIRT-1 expression in obese septic mice; the same changes were found in human umbilical vein endothelial cells treated with resveratrol *in vitro* suggesting that resveratrol can reduce microvascular inflammation by increasing the expression of SIRT-1 (Xianfeng Wang et al., 2015).

## Immune System

In addition to the excessive inflammatory response represented by the overproduction of inflammatory mediators, the body enters a complex state of immune dysfunction during sepsis development and progression. This is characterized by reduced anti-infective immune defense abilities that are reflected in the decreased phagocytic and bactericidal activities and inhibition of antigen-presentation function (Kumar 2020). As innate immunomodulatory cells, macrophages play an important role during sepsis. Several studies have shown that resveratrol can regulate the activity of macrophages, suggesting a protective effect against immune dysfunction in sepsis.

Ma et al. (2017) demonstrated that resveratrol can inhibit macrophage activation by inhibiting the expression of mir-155 and upregulating cytokine signal transduction inhibitor 1. Resveratrol could also reduce the expression levels of the pro-inflammatory factors TNF- $\alpha$  and IL-6. This may be due to its inhibition of the phosphorylation of mitogen-activated protein kinases (MAPKs) and STAT1/3. Moreover, resveratrol can inhibit TRAF6 expression and the ubiquitination of macrophages induced by LPS while also weakening the TLR4-TRAF6, MAPK, and Akt pathways induced by LPS (Jakus et al., 2013). Moreover, resveratrol was reported to inhibit the expression of cyclooxygenase-2 induced by NF- $\kappa$ B and LPS, which was also related to the inhibition of TRIF-TBK1-RIP1 signaling (Youn et al., 2005). Sebai et al. (2010) confirmed that resveratrol may play an antioxidant role through a TRIF-dependent pathway.

In addition, Wang et al. (2020) showed that resveratrol limited the activation of important signal molecules (PLD, SphK1, ERK1/2, and NF- $\kappa$ B) stimulated by LPS at different time points during sepsis induction and progression. In the early stage of sepsis (within 1 h), resveratrol reduced cytokine production by inhibiting PLD and downstream NF- $\kappa$ B and ERK signaling. Throughout the course of the disease (exposure for 4 h or more), resveratrol was able to reduce MyD88-related autophagy, although the direct relationship between the two remains unclear. Resveratrol has also been shown to improve lymphocyte DNA damage in septic rats through antioxidation effects (Aydin et al., 2013).

## Gastrointestinal Tract

*In vivo* animal studies have shown that polyphenol extracts can reduce the severity of colitis by modifying various intracellular signal cascades in the intestinal epithelium and exhibiting anti-inflammatory effects (Romier et al., 2009). Similarly, resveratrol improved ileal smooth muscle reactivity in septic rats (Gacar et al., 2012).

## Adrenal Gland

Endotoxins lead to adrenal oxidative stress and excessive production of NO, which causes adrenocortical dysfunction (Chang-Nan Wang et al., 2015). Resveratrol treatment significantly inhibited iNOS expression, NO production, and peroxynitrite formation induced by endotoxemia and reduced

LPS-induced adrenal oxidative stress, as evidenced by a decrease in MDA and an increase in various antioxidant biomarkers (T-AOC, CAT, and SOD activity). In addition, resveratrol (Duan et al., 2016), as an agonist of SIRT-1, reversed the LPS-induced downregulation of the adrenocorticotropin receptor and SIRT-1 as well as the weak adrenocortical response to corticotropin. Resveratrol also protects against the adrenocortical insufficiency associated with endotoxemia by inhibiting oxidation/nitric stress. These findings support the therapeutic potential of resveratrol in alleviating adrenocortical dysfunction caused by oxidative/nitric stress injuries in sepsis.

## CLINICAL TRIALS

Resveratrol is currently being explored in hundreds of clinical trials involving the nervous, respiratory, and endocrine systems as well as other domains.

Resveratrol supplementation may improve glycated hemoglobin in the short term in the clinical management of diabetes mellitus (Zeraattalab-Motlagh et al., 2021). Resveratrol also improves blood sugar control and lowers blood pressure (Nyambuya et al., 2020). In addition, resveratrol supplementation has been found to significantly reduce C-reactive protein levels in patients with type 2 diabetes (Hosseini et al., 2020).

Meta-analyses of patients with metabolic syndrome and related disorders have yielded seemingly contradictory results (Asgary et al., 2019; Akbari et al., 2020; Tabrizi et al., 2020). Therefore, more randomized controlled trials (RCTs) are needed to supplement and validate these findings in the future. In a meta-analysis of obese patients, resveratrol intake significantly reduced body weight, BMI and fat mass, and significantly increased lean body mass but did not affect leptin and adiponectin levels (Tabrizi et al., 2020). In addition, a meta-analysis involving 11 clinical studies showed that resveratrol supplementation was effective in reducing alveolar bone loss and preventing the clinical development of periodontal disease (Andrade et al., 2019). Regular resveratrol supplementation also demonstrated a positive effect on bone mineral density in postmenopausal women (Wong et al., 2020). In patients with polycystic ovary, 1,500 mg of resveratrol per day significantly reduced ovarian and adrenal androgen levels (Banaszewska et al., 2016). Resveratrol supplementation also showed effectiveness against a number of cancers including breast cancer (Zhu et al., 2012), liver cancer (Howells et al., 2011), and colorectal cancer (Patel et al., 2010). These results need to be validated in the future through larger RCTs. There are currently no trials available discussing the potential of resveratrol in sepsis treatment; therefore, further exploration is needed in the future.

## SAFETY

Resveratrol is divided into cis and trans structures, with the more stable trans structure found in nature. Due to differences

in bioavailability and pharmacokinetics, current studies suggest that oral resveratrol reduces the level of lipid peroxidation in the small intestine and colon due to LPS-induced sepsis but has no effect on inflammatory markers (Larrosa et al., 2011), which suggests that the optimal route of administration should be selected according to the bioavailability and target organ.

Hebbar et al. (2005) administered resveratrol to CD rats at high doses. This resulted in varying degrees of dehydration, dyspnea, nephrotoxicity, and increased liver enzymes in serum indicating that resveratrol has a certain degree of toxicity at high doses. Johnson et al. (2011) confirmed that high-dose resveratrol can increase liver bilirubin levels, demonstrating subchronic oral toxicity. However, the doses tested in these studies are much higher than the current clinical dose (500–1,000 mg/day). In addition, the oral absorbance of resveratrol was estimated to be at least 75%; however, due to the rapid and extensive metabolism, biological availability is poor (Ait-Oufella et al., 2015). Therefore, the bioavailability of resveratrol remains a major concern for the development of medical products and technology. Scientists have been exploring updated *trans*-resveratrol delivery mechanisms to improve solubility and bioavailability, including methylated resveratrol analogs (Kang et al., 2014), resveratrol particle system (Peng et al., 2010), and vesicle system (Pangeni et al., 2014) carriers.

## PROSPECTS FOR THE FUTURE

Resveratrol exerts a variety of sepsis-related protective mechanisms. The therapeutic potential of resveratrol has attracted the attention of researchers as sepsis remains a global problem. Many studies have been carried out in sepsis cell cultures and animal models; however, numerous hurdles still need to be overcome so that resveratrol could be utilized clinically. These hurdles include bioavailability, dose optimization, and side effect reduction. Currently, large-scale, clinical application of resveratrol requires more pre-clinical and clinical studies. Also, the preparation process of resveratrol somewhat restricts its development and application. For example, the bioactivity of chemically synthesized resveratrol is not as good as that of natural products, but the cost and purity of natural products pose a challenge. Some of these hurdles could be tackled via modern drug development technologies. For example, precursor drugs could be synthesized using nanomaterial coating while also chemically modifying the active ingredient, resveratrol. This would allow its release across the intestinal tract to specific target organs improving its bioavailability and providing the possibility to improve the research status of resveratrol and further their clinical application. Thus, the comprehensive mechanism and clinical application of resveratrol remain important topics of exploration in future research.

## AUTHOR CONTRIBUTIONS

JL, XZ, RL, SL and XL wrote the original draft. FZ, YL, FY, and LW undertook validation, writing, review, and editing. XH, YPL undertook writing, review, and editing. All authors contributed to the article and approved the submitted version.

## REFERENCES

- Ait-Oufella, H., Bourcier, S., Lehoux, S., and Guidet, B. (2015). Microcirculatory Disorders during Septic Shock. *Curr. Opin. Crit. Care* 21 (4), 271–275. doi:10.1097/MCC.0000000000000217
- Akbari, M., Tamtaji, O. R., Lankarani, K. B., Tabrizi, R., Dadgostar, E., Haghghat, N., et al. (2020). The Effects of Resveratrol on Lipid Profiles and Liver Enzymes in Patients with Metabolic Syndrome and Related Disorders: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Lipids Health Dis.* 19 (1), 25. doi:10.1186/s12944-020-1198-x
- An, R., Zhao, L., Xu, J., Xi, C., Li, H., Shen, G., et al. (2016). Resveratrol Alleviates Sepsis-induced Myocardial Injury in Rats by Suppressing Neutrophil Accumulation, the Induction of TNF- $\alpha$  and Myocardial Apoptosis via Activation of Sirt1. *Mol. Med. Rep.* 14 (6), 5297–5303. doi:10.3892/mmr.2016.5861
- Andrade, E. F., Orlando, D. R., Araújo, A. M. S., de Andrade, J. N. B. M., Azzi, D. V., de Lima, R. R., et al. (2019). Can Resveratrol Treatment Control the Progression of Induced Periodontal Disease? A Systematic Review and Meta-Analysis of Preclinical Studies. *Nutrients* 11 (5), 953. doi:10.3390/nu11050953
- Arunachalam, G., Yao, H., Sundar, I. K., Caito, S., and Rahman, I. (2010). SIRT1 Regulates Oxidant- and Cigarette Smoke-Induced eNOS Acetylation in Endothelial Cells: Role of Resveratrol. *Biochem. Biophys. Res. Commun.* 393 (1), 66–72. doi:10.1016/j.bbrc.2010.01.080
- Asgary, S., Karimi, R., Momtaz, S., Naseri, R., and Farzaei, M. H. (2019). Effect of Resveratrol on Metabolic Syndrome Components: A Systematic Review and Meta-Analysis. *Rev. Endocr. Metab. Disord.* 20 (2), 173–186. doi:10.1007/s11154-019-09494-z
- Ashrafzadeh, M., Rafiei, H., Mohammadinejad, R., Farkhondeh, T., and Samarghandian, S. (2021). Anti-tumor Activity of Resveratrol against Gastric Cancer: a Review of Recent Advances with an Emphasis on Molecular Pathways. *Cancer Cel Int* 21 (1), 66. doi:10.1186/s12935-021-01773-7
- Aydin, S., Bacanlı, M., Taner, G., Şahin, T., Başaran, A., and Başaran, N. (2013). Protective Effects of Resveratrol on Sepsis-Induced DNA Damage in the Lymphocytes of Rats. *Hum. Exp. Toxicol.* 32 (10), 1048–1057. doi:10.1177/0960327112467047
- Bagshaw, S. M., Lapinsky, S., Dial, S., Arabi, Y., Dodek, P., Wood, G., et al. (2009). Acute Kidney Injury in Septic Shock: Clinical Outcomes and Impact of Duration of Hypotension Prior to Initiation of Antimicrobial Therapy. *Intensive Care Med.* 35 (5), 871–881. doi:10.1007/s00134-008-1367-2
- Bai, T., Hu, X., Zheng, Y., Wang, S., Kong, J., and Cai, L. (2016). Resveratrol Protects against Lipopolysaccharide-Induced Cardiac Dysfunction by Enhancing SERCA2a Activity through Promoting the Phospholamban Oligomerization. *Am. J. Physiol. Heart Circ. Physiol.* 311 (4), H1051–H1062. doi:10.1152/ajpheart.00296.2016
- Banaszewska, B., Wrotyńska-Barczyńska, J., Spaczynski, R. Z., Pawelczyk, L., and Duleba, A. J. (2016). Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-Blind, Randomized, Placebo-Controlled Trial. *J. Clin. Endocrinol. Metab.* 101 (11), 4322–4328. doi:10.1210/jc.2016-1858
- Bobermin, L. D., Roppa, R. H. A., and Quincozes-Santos, A. (2019). Adenosine Receptors as a New Target for Resveratrol-Mediated Glioprotection. *Biochim. Biophys. Acta Mol. Basis Dis.* 1865 (3), 634–647. doi:10.1016/j.bbdis.2019.01.004
- Campagna, M., and Rivas, C. (2010). Antiviral Activity of Resveratrol. *Biochem. Soc. Trans.* 38 (1), 50–53. doi:10.1042/BST0380050
- Cecconi, M., Evans, L., Levy, M., and Rhodes, A. (2018). Sepsis and Septic Shock. *Lancet* 392 (10141), 75–87. doi:10.1016/S0140-6736(18)30696-2
- Chen, L., Yang, S., Zumbun, E. E., Guan, H., Nagarkatti, P. S., and Nagarkatti, M. (2015). Resveratrol Attenuates Lipopolysaccharide-Induced Acute Kidney Injury by Suppressing Inflammation Driven by Macrophages. *Mol. Nutr. Food Res.* 59 (5), 853–864. doi:10.1002/mnfr.201400819
- Dai, H., Sinclair, D. A., Ellis, J. L., and Steegborn, C. (2018). Sirtuin Activators and Inhibitors: Promises, Achievements, and Challenges. *Pharmacol. Ther.* 188, 140–154. doi:10.1016/j.pharmthera.2018.03.004
- Duan, G.-L., Wang, C.-N., Liu, Y.-J., Yu, Q., Tang, X.-L., Ni, X., et al. (2016). Resveratrol Alleviates Endotoxemia-Associated Adrenal Insufficiency by Suppressing Oxidative/nitrative Stress. *Endocr. J.* 63 (6), 569–580. doi:10.1507/endocrj.15-0610
- Fani, F., Regolisti, G., Delsante, M., Cantaluppi, V., Castellano, G., Gesualdo, L., et al. (2018). Recent Advances in the Pathogenetic Mechanisms of Sepsis-Associated Acute Kidney Injury. *J. Nephrol.* 31 (3), 351–359. doi:10.1007/s40620-017-0452-4
- Farkhondeh, T., Folgado, S. L., Pourbagher-Shahri, A. M., Ashrafzadeh, M., and Samarghandian, S. (2020). The Therapeutic Effect of Resveratrol: Focusing on the Nrf2 Signaling Pathway. *Biomed. Pharmacother.* 127, 110234. doi:10.1016/j.biopha.2020.110234
- Filardo, S., Di Pietro, M., Mastromarino, P., and Sessa, R. (2020). Therapeutic Potential of Resveratrol against Emerging Respiratory Viral Infections. *Pharmacol. Ther.* 214, 107613. doi:10.1016/j.pharmthera.2020.107613
- Flierl, M. A., Rittirsch, D., Huber-Lang, M. S., Sarma, J. V., and Ward, P. A. (2008). Molecular Events in the Cardiomyopathy of Sepsis. *Mol. Med.* 14 (5), 327–336. doi:10.2119/2007-00130.Flierl
- Gacar, N., Gocmez, S., Utkan, T., Gacar, G., Komsuoglu, I., Tugay, M., et al. (2012). Effects of Resveratrol on Ileal Smooth Muscle Reactivity in Polymicrobial Sepsis Model. *J. Surg. Res.* 174 (2), 339–343. doi:10.1016/j.jss.2010.12.015
- García-Pérez, M.-E., Royer, M., Herbette, G., Desjardins, Y., Pouliot, R., and Stévanovic, T. (2012). Picea Mariana Bark: A New Source of Trans-resveratrol and Other Bioactive Polyphenols. *Food Chem.* 135 (3), 1173–1182. doi:10.1016/j.foodchem.2012.05.050
- Goffton, T. E., and Young, G. B. (2012). Sepsis-associated Encephalopathy. *Nat. Rev. Neurol.* 8 (10), 557–566. doi:10.1038/nrneuro.2012.183
- Hao, E., Lang, F., Chen, Y., Zhang, H., Cong, X., Shen, X., et al. (2013). Resveratrol Alleviates Endotoxin-Induced Myocardial Toxicity via the Nrf2 Transcription Factor. *PLoS one* 8 (7), e69452. doi:10.1371/journal.pone.0069452
- Hebbar, V., Shen, G., Hu, R., Kim, B. R., Chen, C., Korytko, P. J., et al. (2005). Toxicogenomics of Resveratrol in Rat Liver. *Life Sci.* 76 (20), 2299–2314. doi:10.1016/j.lfs.2004.10.039
- Holthoff, J. H., Wang, Z., Seely, K. A., Gokden, N., and Mayeux, P. R. (2012). Resveratrol Improves Renal Microcirculation, Protects the Tubular Epithelium, and Prolongs Survival in a Mouse Model of Sepsis-Induced Acute Kidney Injury. *Kidney Int.* 81 (4), 370–378. doi:10.1038/ki.2011.347
- Holthoff, J. H., Wang, Z., Seely, K. A., and Mayeux, P. R. (2011). Resveratrol Improves Renal Blood Flow and Microcirculation in the Kidney during Experimental Septic Shock in Mice. *FASEB J.* 25 (S1), 639.620. doi:10.1038/ki.2011.347
- Hosseini, H., Koushki, M., Khodabandehloo, H., Fathi, M., Panahi, G., Teimouri, M., et al. (2020). The Effect of Resveratrol Supplementation on C-Reactive Protein (CRP) in Type 2 Diabetic Patients: Results from a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Complement. Ther. Med.* 49, 102251. doi:10.1016/j.ctim.2019.102251
- Hoste, E. A. J., Kellum, J. A., Selby, N. M., Zarbock, A., Palevsky, P. M., Bagshaw, S. M., et al. (2018). Global Epidemiology and Outcomes of Acute Kidney Injury. *Nat. Rev. Nephrol.* 14 (10), 607–625. doi:10.1038/s41581-018-0052-0
- Howells, L. M., Berry, D. P., Elliott, P. J., Jacobson, E. W., Hoffmann, E., Hegarty, B., et al. (2011). Phase I Randomized, Double-Blind Pilot Study of Micronized Resveratrol (SRT501) in Patients with Hepatic Metastases-Safety,

## FUNDING

Funding was provided by the Key research and development project of Science and Technology of Sichuan Province (Grant no. 20ZDYF 1870) and the Chengdu Technology Innovation Research and Development Project (2021-YF05-02246-SN).



- Pharmacokinetics, and Pharmacodynamics. *Cancer Prev. Res. (Phila)* 4 (9), 1419–1425. doi:10.1158/1940-6207.CAPR-11-0148
- Hwang, J. W., Yao, H., Caito, S., Sundar, I. K., and Rahman, I. (2013). Redox Regulation of SIRT1 in Inflammation and Cellular Senescence. *Free Radic. Biol. Med.* 61, 95–110. doi:10.1016/j.freeradbiomed.2013.03.015
- Jakus, P. B., Kalman, N., Antus, C., Radnai, B., Tucek, Z., Gallyas, F., Jr, et al. (2013). TRAF6 Is Functional in Inhibition of TLR4-Mediated NF-Kb Activation by Resveratrol. *J. Nutr. Biochem.* 24 (5), 819–823. doi:10.1016/j.jnutbio.2012.04.017
- Ji, Z., Li, Y., and Sun, G. (2016). Resveratrol Attenuates Myocardial Injury in Septic Rats via Inhibition of the JAK2/STAT3 Signaling Pathway. *Int. J. Clin. Exp. Med.* 9, 1724–1731.
- Johnson, W. D., Morrissey, R. L., Osborne, A. L., Kapetanovic, I., Crowell, J. A., Muzzio, M., et al. (2011). Subchronic Oral Toxicity and Cardiovascular Safety Pharmacology Studies of Resveratrol, a Naturally Occurring Polyphenol with Cancer Preventive Activity. *Food Chem. Toxicol.* 49 (12), 3319–3327. doi:10.1016/j.fct.2011.08.023
- Kang, S. Y., Lee, J. K., Choi, O., Kim, C. Y., Jang, J. H., Hwang, B. Y., et al. (2014). Biosynthesis of Methylated Resveratrol Analogs through the Construction of an Artificial Biosynthetic Pathway in *E. coli*. *BMC Biotechnol.* 14 (1), 67–11. doi:10.1186/1472-6750-14-67
- Karunakaran, D., Thrush, A. B., Nguyen, M. A., Richards, L., Geoffrion, M., Singaravelu, R., et al. (2015). Macrophage Mitochondrial Energy Status Regulates Cholesterol Efflux and Is Enhanced by Anti-miR33 in Atherosclerosis. *Circ. Res.* 117 (3), 266–278. doi:10.1161/CIRCRESAHA.117.305624
- Kitada, M., Ogura, Y., and Koya, D. (2016). The Protective Role of Sirt1 in Vascular Tissue: its Relationship to Vascular Aging and Atherosclerosis. *Aging (Albany NY)* 8 (10), 2290–2307. doi:10.18632/aging.101068
- Kolgazi, M., Sener, G., Cetinel, S., Gedik, N., and Alican, I. (2006). Resveratrol Reduces Renal and Lung Injury Caused by Sepsis in Rats. *J. Surg. Res.* 134 (2), 315–321. doi:10.1016/j.jss.2005.12.027
- Kumar, V. (2020). Sepsis Roadmap: What We Know, what We Learned, and where We Are Going. *Clin. Immunol.* 210, 108264. doi:10.1016/j.clim.2019.108264
- Larrosa, M., Azorín-Ortuño, M., Yañez-Gascón, M. J., García-Conesa, M. T., Tomás-Barberán, F., and Espín, J. C. (2011). Lack of Effect of Oral Administration of Resveratrol in LPS-Induced Systemic Inflammation. *Eur. J. Nutr.* 50 (8), 673–680. doi:10.1007/s00394-011-0178-3
- L'Heureux, M., Sternberg, M., Brath, L., Turlington, J., and Kashiouris, M. G. (2020). Sepsis-induced Cardiomyopathy: a Comprehensive Review. *Curr. Cardiol. Rep.* 22 (5), 35. doi:10.1007/s11886-020-01277-2
- Liao, M. T., Wu, C. C., Wu, S. V., Lee, M. C., Hu, W. C., Tsai, K. W., et al. (2021). Resveratrol as an Adjunctive Therapy for Excessive Oxidative Stress in Aging COVID-19 Patients. *Antioxidants (Basel)* 10 (9), 1440. doi:10.3390/antiox10091440
- Liu, X., Wen, M., Han, Y., Ding, H., Chen, S., Li, Y., et al. (2020). Mechanism of Resveratrol on Ameliorating the Cognitive Dysfunction Induced by Sepsis Associated Encephalopathy in Rats. *Zhonghua wei Zhong Bing ji jiu yi xue* 32 (10), 1189–1193. doi:10.3760/cma.j.cn121430-20200720-00531
- Lu, C. C., Lai, H. C., Hsieh, S. C., and Chen, J. K. (2008). Resveratrol Ameliorates Serratia marcescens-induced Acute Pneumonia in Rats. *Wiley Online Libr.* 83, 1028–1037. doi:10.1189/jlb.0907647
- Luo, C. J., Luo, F., Bu, Q. D., Jiang, W., Zhang, W., Liu, X. M., et al. (2020). Protective Effects of Resveratrol on Acute Kidney Injury in Rats with Sepsis. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub* 164 (1), 49–56. doi:10.5507/bp.2019.006
- Ma, C., Wang, Y., Shen, A., and Cai, W. (2017). Resveratrol Upregulates SOCS1 Production by Lipopolysaccharide-Stimulated RAW264.7 Macrophages by Inhibiting miR-155. *Int. J. Mol. Med.* 39 (1), 231–237. doi:10.3892/ijmm.2016.2802
- Matthay, M. A., Zemans, R. L., Zimmerman, G. A., Arabi, Y. M., Beitler, J. R., Mercat, A., et al. (2019). Acute Respiratory Distress Syndrome. *Nat. Rev. Dis. Primers* 5 (1), 18–22. doi:10.1038/s41572-019-0069-0
- Nadtochiy, S. M., Redman, E., Rahman, I., and Brookes, P. S. (2011a). Lysine Deacetylation in Ischaemic Preconditioning: the Role of SIRT1. *Cardiovasc. Res.* 89 (3), 643–649. doi:10.1093/cvr/cvq287
- Nadtochiy, S. M., Yao, H., McBurney, M. W., Gu, W., Guarente, L., Rahman, I., et al. (2011b). SIRT1-mediated Acute Cardioprotection. *Am. J. Physiol. Heart Circ. Physiol.* 301 (4), H1506–H1512. doi:10.1152/ajpheart.00587.2011
- Nyambuya, T. M., Nkambule, B. B., Mazibuko-Mbeje, S. E., Mxinwa, V., Mokgalaboni, K., Orlando, P., et al. (2020). A Meta-Analysis of the Impact of Resveratrol Supplementation on Markers of Renal Function and Blood Pressure in Type 2 Diabetic Patients on Hypoglycemic Therapy. *Molecules* 25 (23), 5645. doi:10.3390/molecules25235645
- Pangeni, R., Sahni, J. K., Ali, J., Sharma, S., and Baboota, S. (2014). Resveratrol: Review on Therapeutic Potential and Recent Advances in Drug Delivery. *Expert Opin. Drug Deliv.* 11 (8), 1285–1298. doi:10.1517/17425247.2014.919253
- Patel, K. R., Brown, V. A., Jones, D. J., Britton, R. G., Hemingway, D., Miller, A. S., et al. (2010). Clinical Pharmacology of Resveratrol and its Metabolites in Colorectal Cancer Patients. *Cancer Res.* 70 (19), 7392–7399. doi:10.1158/0008-5472.CAN-10-2027
- Peng, H., Xiong, H., Li, J., Xie, M., Liu, Y., Bai, C., et al. (2010). Vanillin Cross-Linked Chitosan Microspheres for Controlled Release of Resveratrol. *Food Chem.* 121 (1), 23–28. doi:10.1016/j.foodchem.2009.11.085
- Price, N. L., Gomes, A. P., Ling, A. J., Duarte, F. V., Martin-Montalvo, A., North, B. J., et al. (2012). SIRT1 Is Required for AMPK Activation and the Beneficial Effects of Resveratrol on Mitochondrial Function. *Cell Metab* 15 (5), 675–690. doi:10.1016/j.cmet.2012.04.003
- Quan, H., Yin, M., Kim, J., Jang, E. A., Yang, S. H., Bae, H. B., et al. (2021). Resveratrol Suppresses the Reprogramming of Macrophages into an Endotoxin-Tolerant State through the Activation of AMP-Activated Protein Kinase. *Eur. J. Pharmacol.* 899, 173993. doi:10.1016/j.ejphar.2021.173993
- Ratiani, L., Gamkrelidze, M., Khuchua, E., Khutsishvili, T., Intskirveli, N., and Vardosanidze, K. (2015). Altered Microcirculation in Septic Shock. *Georgian Med. News.* 16–24.
- Romier, B., Schneider, Y. J., Larondelle, Y., and During, A. (2009). Dietary Polyphenols Can Modulate the Intestinal Inflammatory Response. *Nutr. Rev.* 67 (7), 363–378. doi:10.1111/j.1753-4887.2009.00210.x
- Rubinfeld, G. D., Caldwell, E., Peabody, E., Weaver, J., Martin, D. P., Neff, M., et al. (2005). Incidence and Outcomes of Acute Lung Injury. *N. Engl. J. Med.* 353 (16), 1685–1693. doi:10.1056/NEJMoa050333
- Sanders, T. H., McMichael, R. W., and Hendrix, K. W. (2000). Occurrence of Resveratrol in Edible Peanuts. *J. Agric. Food Chem.* 48 (4), 1243–1246. doi:10.1021/jf990737b
- Sebai, H., Ben-Attia, M., Sani, M., Aouani, E., and Ghanem-Boughanmi, N. (2009). Protective Effect of Resveratrol in Endotoxemia-Induced Acute Phase Response in Rats. *Arch. Toxicol.* 83 (4), 335–340. doi:10.1007/s00204-008-0348-0
- Sebai, H., Ristorcelli, E., Sbarra, V., Hovsepian, S., Fayet, G., Aouani, E., et al. (2010). Protective Effect of Resveratrol against LPS-Induced Extracellular Lipoperoxidation in AR42J Cells Partly via a Myd88-dependent Signaling Pathway. *Arch. Biochem. Biophys.* 495 (1), 56–61. doi:10.1016/j.abb.2009.12.019
- Sebai, H., Sani, M., Aouani, E., and Ghanem-Boughanmi, N. (2011). Cardioprotective Effect of Resveratrol on Lipopolysaccharide-Induced Oxidative Stress in Rat. *Drug Chem. Toxicol.* 34 (2), 146–150. doi:10.3109/01480545.2010.494666
- Shakibaie, M., Harikumar, K. B., and Aggarwal, B. B. (2009). Resveratrol addiction: to die or not to die. *Mol. Nutr. Food Res.* 53 (1), 115–128. doi:10.1002/mnfr.200800148
- Shang, X., Lin, K., Yu, R., Zhu, P., Zhang, Y., Wang, L., et al. (2019). Resveratrol Protects the Myocardium in Sepsis by Activating the Phosphatidylinositol 3-Kinases (PI3K)/AKT/Mammalian Target of Rapamycin (mTOR) Pathway and Inhibiting the Nuclear Factor-Kb (NF-Kb) Signaling Pathway. *Med. Sci. Monit.* 25, 9290–9298. doi:10.12659/MSM.918369
- Shankar-Hari, M., Harrison, D. A., and Rowan, K. M. (2016a). Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology-A Cohort Study Illustrating the Need for Standardized Reporting. *Crit. Care Med.* 44 (12), 2223–2230. doi:10.1097/CCM.0000000000001876
- Shankar-Hari, M., Phillips, G. S., Levy, M. L., Seymour, C. W., Liu, V. X., Deutschman, C. S., et al. (2016b). 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* 315 (8), 775–787. doi:10.1001/jama.2016.0289

- Shapiro, H., Lev, S., Cohen, J., and Singer, P. (2009). Polyphenols in the Prevention and Treatment of Sepsis Syndromes: Rationale and Pre-clinical Evidence. *Nutrition* 25 (10), 981–997. doi:10.1016/j.nut.2009.02.010
- Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., et al. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 315 (8), 801–810. doi:10.1001/jama.2016.0287
- Smeding, L., Leong-Poi, H., Hu, P., Shan, Y., Haitsma, J. J., Horvath, E., et al. (2012). Salutary Effect of Resveratrol on Sepsis-Induced Myocardial Depression. *Crit. Care Med.* 40 (6), 1896–1907. doi:10.1097/CCM.0b013e31824e1370
- Sui, D.-m., Xie, Q., Yi, W.-j., Gupta, S., Yu, X.-y., Li, J.-b., et al. (2016). Resveratrol Protects against Sepsis-Associated Encephalopathy and Inhibits the NLRP3/IL-1 $\beta$  axis in Microglia. *Mediators Inflamm.* 2016, 1045657. doi:10.1155/2016/1045657
- Tabrizi, R., Tamtaji, O. R., Lankarani, K. B., Akbari, M., Dadgostar, E., Dabbaghmanesh, M. H., et al. (2020). The Effects of Resveratrol Intake on Weight Loss: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Crit. Rev. Food Sci. Nutr.* 60 (3), 375–390. doi:10.1080/10408398.2018.1529654
- van der Poll, T., van de Veerndonk, F. L., Scicluna, B. P., and Netea, M. G. (2017). The Immunopathology of Sepsis and Potential Therapeutic Targets. *Nat. Rev. Immunol.* 17 (7), 407–420. doi:10.1038/nri.2017.36
- Varatharaj, A., and Galea, I. (2017). The Blood-Brain Barrier in Systemic Inflammation. *Brain Behav. Immun.* 60, 1–12. doi:10.1016/j.bbi.2016.03.010
- Vinciguerra, M., Santini, M. P., Martinez, C., Paziienza, V., Claycomb, W. C., Giuliani, A., et al. (2012). mIGF-1/JNK1/SirT1 Signaling Confers protection against Oxidative Stress in the Heart. *Aging cell* 11 (1), 139–149. doi:10.1111/j.1474-9726.2011.00766.x
- Wang, B., Bellot, G. L., Iskandar, K., Chong, T. W., Goh, F. Y., Tai, J. J., et al. (2020). Resveratrol Attenuates TLR-4 Mediated Inflammation and Elicits Therapeutic Potential in Models of Sepsis. *Sci. Rep.* 10 (1), 18837. doi:10.1038/s41598-020-74578-9
- Wang, C. N., Duan, G. L., Liu, Y. J., Yu, Q., Tang, X. L., Zhao, W., et al. (2015). Overproduction of Nitric Oxide by Endothelial Cells and Macrophages Contributes to Mitochondrial Oxidative Stress in Adrenocortical Cells and Adrenal Insufficiency during Endotoxemia. *Free Radic. Biol. Med.* 83, 31–40. doi:10.1016/j.freeradbiomed.2015.02.024
- Wang, H., Zhu, S., Zhou, R., Li, W., and Sama, A. E. (2008). Therapeutic Potential of HMGB1-Targeting Agents in Sepsis. *Expert Rev. Mol. Med.* 10, e32. doi:10.1017/s1462399408000884
- Wang, N., Mao, L., Yang, L., Zou, J., Liu, K., Liu, M., et al. (2017). Resveratrol Protects against Early Polymicrobial Sepsis-Induced Acute Kidney Injury through Inhibiting Endoplasmic Reticulum Stress-Activated NF-Kb Pathway. *Oncotarget* 8 (22), 36449–36461. doi:10.18632/oncotarget.16860
- Wang, X., Buechler, N. L., Yoza, B. K., McCall, C. E., and Vachharajani, V. T. (2015). Resveratrol Attenuates Microvascular Inflammation in Sepsis via SIRT-1-Induced Modulation of Adhesion Molecules in Ob/ob Mice. *Obesity (Silver Spring)* 23 (6), 1209–1217. doi:10.1002/oby.21086
- Wang, X. Q., Zhang, Y. P., Zhang, L. M., Feng, N. N., Zhang, M. Z., Zhao, Z. G., et al. (2017). Resveratrol Enhances Vascular Reactivity in Mice Following Lipopolysaccharide challenge via the RhoA-ROCK-MLCP Pathway. *Exp. Ther. Med.* 14 (1), 308–316. doi:10.3892/etm.2017.4486
- Wang, Y., Cui, H., Niu, F., Liu, S. L., Li, Y., Zhang, L. M., et al. (2018a). Effect of Resveratrol on Blood Rheological Properties in LPS-Challenged Rats. *Front. Physiol.* 9, 1202. doi:10.3389/fphys.2018.01202
- Wang, Y., Wang, X., Zhang, L., and Zhang, R. (2018b). Alleviation of Acute Lung Injury in Rats with Sepsis by Resveratrol via the Phosphatidylinositol 3-kinase/nuclear Factor-Erythroid 2 Related Factor 2/heme Oxygenase-1 (PI3K/Nrf2/HO-1) Pathway. *Med. Sci. Monit.* 24, 3604–3611. doi:10.12659/MSM.910245
- Wong, R. H., Thuang Zaw, J. J., Xian, C. J., and Howe, P. R. (2020). Regular Supplementation with Resveratrol Improves Bone Mineral Density in Postmenopausal Women: A Randomized, Placebo-Controlled Trial. *J. Bone Miner Res.* 35 (11), 2121–2131. doi:10.1002/jbmr.4115
- Xu, S., Gao, Y., Zhang, Q., Wei, S., Chen, Z., Dai, X., et al. (2016). SIRT1/3 Activation by Resveratrol Attenuates Acute Kidney Injury in a Septic Rat Model. *Oxidative Med. Cell Longevity* 2016, 7296092. doi:10.1155/2016/7296092
- Xu, W., Lu, Y., Yao, J., Li, Z., Chen, Z., Wang, G., et al. (2014). Novel Role of Resveratrol: Suppression of High-Mobility Group Protein Box 1 Nucleocytoplasmic Translocation by the Upregulation of Sirtuin 1 in Sepsis-Induced Liver Injury. *Shock* 42 (5), 440–447. doi:10.1097/SHK.0000000000000225
- Yang, L., Zhang, Z., Zhuo, Y., Cui, L., Li, C., Li, D., et al. (2018). Resveratrol Alleviates Sepsis-Induced Acute Lung Injury by Suppressing Inflammation and Apoptosis of Alveolar Macrophage Cells. *Am. J. Transl Res.* 10 (7), 1961–1975.
- Youn, H. S., Lee, J. Y., Fitzgerald, K. A., Young, H. A., Akira, S., and Hwang, D. H. (2005). Specific Inhibition of MyD88-independent Signaling Pathways of TLR3 and TLR4 by Resveratrol: Molecular Targets Are TBK1 and RIP1 in TRIF Complex. *J. Immunol.* 175 (5), 3339–3346. doi:10.4049/jimmunol.175.5.3339
- Zeraattalab-Motlagh, S., Jayedi, A., and Shab-Bidar, S. (2021). The Effects of Resveratrol Supplementation in Patients with Type 2 Diabetes, Metabolic Syndrome, and Nonalcoholic Fatty Liver Disease: an Umbrella Review of Meta-Analyses of Randomized Controlled Trials. *Am. J. Clin. Nutr.* 114 (5), 1675–1685. doi:10.1093/ajcn/nqab250
- Zhang, H. X., Duan, G. L., Wang, C. N., Zhang, Y. Q., Zhu, X. Y., and Liu, Y. J. (2014). Protective Effect of Resveratrol against Endotoxemia-Induced Lung Injury Involves the Reduction of Oxidative/nitrate Stress. *Pulm. Pharmacol. Ther.* 27 (2), 150–155. doi:10.1016/j.pupt.2013.07.007
- Zhang, Z. S., Zhao, H. L., Yang, G. M., Zang, J. T., Zheng, D. Y., Duan, C. Y., et al. (2019). Role of Resveratrol in Protecting Vasodilatation Function in Septic Shock Rats and its Mechanism. *J. Trauma Acute Care Surg.* 87 (6), 1336–1345. doi:10.1097/TA.00000000000002466
- Zhou, J., Yang, D., Liu, K., Hou, L., and Zhang, W. (2019). Systematic Review and Meta-Analysis of the Protective Effect of Resveratrol on Multiple Organ Injury Induced by Sepsis in Animal Models. *Biomed. Rep.* 10 (1), 55–62. doi:10.3892/br.2018.1169
- Zhou, R. R., Zhao, S. S., Zou, M. X., Zhang, P., Zhang, B. X., Dai, X. H., et al. (2011). HMGB1 Cytoplasmic Translocation in Patients with Acute Liver Failure. *BMC Gastroenterol.* 11 (1), 21–11. doi:10.1186/1471-230X-11-21
- Zhu, W., Qin, W., Zhang, K., Rottinghaus, G. E., Chen, Y. C., Kliethermes, B., et al. (2012). Trans-resveratrol Alters Mammary Promoter Hypermethylation in Women at Increased Risk for Breast Cancer. *Nutr. Cancer* 64 (3), 393–400. doi:10.1080/01635581.2012.654926
- Zimmermann-Franco, D. C., Esteves, B., Lacerda, L. M., Souza, I. O., Santos, J. A. D., Pinto, N. C. C., et al. (2018). *In Vitro* and *In Vivo* Anti-inflammatory Properties of Imine Resveratrol Analogues. *Bioorg. Med. Chem.* 26 (17), 4898–4906. doi:10.1016/j.bmc.2018.08.029

**Conflict of 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.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Li, Zeng, Yang, Wang, Luo, Liu, Zeng, Lu, Huang, Lei and Lan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.