

## Review Article

# Anti-Inflammatory and Organ-Protective Effects of Resveratrol in Trauma-Hemorrhagic Injury

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Resveratrol, a natural polyphenolic compound of grape and red wine, owns potential anti-inflammatory effects, which results in the reduction of cytokines overproduction, the inhibition of neutrophil activity, and the alteration of adhesion molecules expression. Resveratrol also possesses antioxidant, anti-coagulation and anti-aging properties, and it may control of cell cycle and apoptosis. Resveratrol has been shown to reduce organ damage following traumatic and shock-like states. Such protective phenomenon is reported to be implicated in a variety of intracellular signaling pathways including the activation of estrogen receptor, the regulation of the sirtuin 1/nuclear factor-kappa B and mitogen-activated protein kinases/hemeoxygenase-1 pathway, and the mediation of proinflammatory cytokines and reactive oxygen species formation and reaction. In the recent studies, resveratrol attenuates hepatocyte injury and improves cardiac contractility due to reduction of proinflammatory mediator expression and ameliorates hypoxia-induced liver and kidney mitochondrial dysfunction following trauma and hemorrhagic injuries. Moreover, through anti-inflammatory effects and antioxidant properties, the resveratrol is believed to protect organ function in trauma-hemorrhagic injury. In this review, the organ-protective and anti-inflammatory effects of resveratrol in trauma-hemorrhagic injury will be discussed.

## 1. Introduction

Resveratrol is a naturally occurring plant antibiotic known as phytoalexins, found in various plants and fruits, especially abundant in grapes and red wine [1, 2]. Previous reports have demonstrated the protective effects of resveratrol in different pathological conditions and experimental models [3–7]. Many clinical studies also indicated the beneficial effects of resveratrol in human diseases [8–13]. A growing body of evidence showed that resveratrol might play potential therapeutic roles in human health by its anti-inflammatory, antioxidant, antiaging, antidiabetic, anticoagulative, and apoptotic properties [1, 7, 14, 15]. Resveratrol attenuates organ injury in trauma-hemorrhagic (T-H) injury through multiple pathways, in which a number of the molecular targets and protective effects of resveratrol have been identified, including the estrogen receptors (ER) [16, 17], the protein kinase B (Akt), the AMP-activated protein kinase

(AMPK) [18, 19], the hemeoxygenase-1 (HO-1) [20–22], the histone/protein deacetylase sirtuin 1 (SIRT1) [23, 24], and nuclear factor-kappa B (NF- $\kappa$ B) [25, 26] (Figure 1).

A variety of laboratory and clinical researches also show that resveratrol may lead to tissue- and organ-protective effects against various injuries [27–33]. Traumatic injury is recognized to induce the excessive production of oxidants and proinflammatory mediators and subsequent development of multiple organ dysfunctions [34–37] and resveratrol has been suggested to have organ-protective effect on trauma and hemorrhagic injuries due to its antioxidative activities and anti-inflammatory effects [18, 20, 38–42]. Trauma-hemorrhagic injury causes excessive production of proinflammatory mediators, cytokines, and chemokines. The enhanced secretion of proinflammatory cytokines is a critical factor in the initiation and perpetuation of organ injury [39, 43, 44]. These cytokines recruit other immune cells including neutrophils, thereby increasing leukocyte activation and

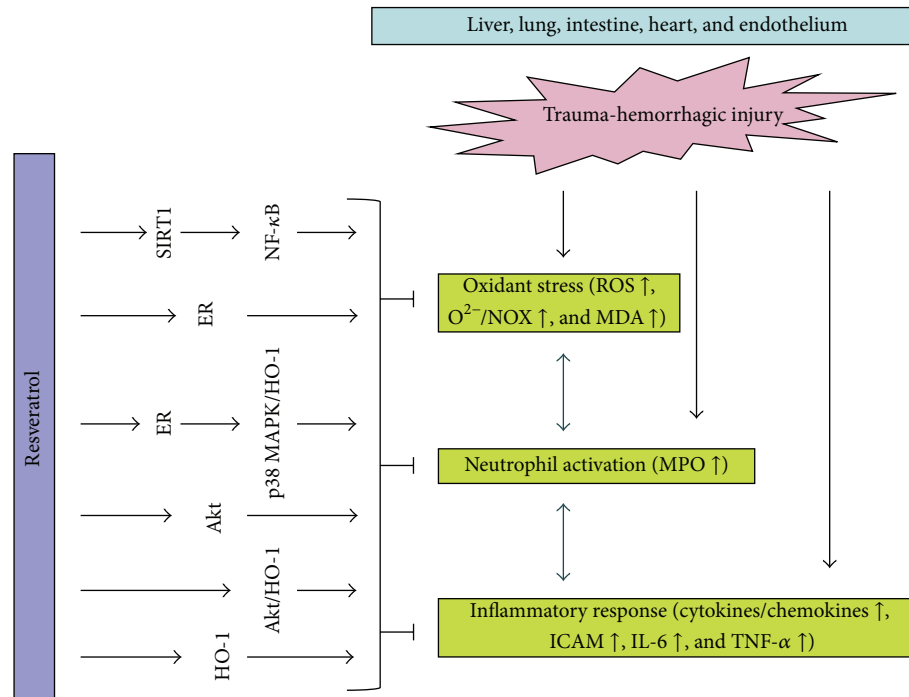


FIGURE 1: The anti-inflammatory and protective pathways of resveratrol in trauma-hemorrhagic injury. ER: estrogen receptor; SIRT1: sirtuin 1; HO-1: hemoxygenase-1; p38 MAPK: p38 mitogen-activated protein kinase; NF- $\kappa$ B: nuclear factor-kappa B; ROS: reactive oxygen species; MDA: malondialdehyde; NOX: NADPH oxidase; MPO: myeloperoxidase; ICAM: intercellular adhesion molecule; IL-6: interleukin 6.

trafficking result in organ injury [45–47]. In this review, we summarize the protective effects and possible mechanisms of resveratrol on the preservation of organ function in T-H injury (Table 1).

## 2. The Pulmonary Protective Effect of Resveratrol in T-H Injury

The activation of neutrophils in T-H injury [39, 47–49] and pulmonary injury is associated with an increased neutrophil accumulation [40, 42]. Neutrophils leave the microcirculation and migrate to matrix proteins or other cells and release mediators, which diffuse across the endothelium and hurt parenchymal cells [46, 47]. The intercellular adhesion molecule 1 (ICAM-1), constitutively present on the surface of endothelial cells, enhances firm adhesion of neutrophils to the vascular endothelium and is markedly upregulated following T-H injury [40, 47, 50]. For example, pulmonary ICAM-1 expression is increased in the lung in T-H shock [40, 47, 51]. The activated neutrophils appear to infiltrate the injured lung in parallel with increased expression of adhesion molecules on endothelial cells and also lead to the elevation of local chemokines/cytokines [40, 47, 51]. Chemotaxis has an important functional response to chemokines and is a key event in the recruitment of neutrophils in inflammation. Cytokine-induced neutrophil chemoattractant 1 (CINC-1) and CINC-3 are members of the IL-8 family and are potent chemoattractants for neutrophils [39, 42]. Moreover, the levels of the CINC-1 and CINC-3 are elevated in T-H injury. Furthermore, convincing evidence has shown that

interleukin 6 (IL-6) plays an important role in organ injuries and is required for the expression of adhesion molecules and release of chemokines [52–54]. IL-6-deficient mice show less neutrophils infiltration and organ damage as compared with wild-type mice under hemorrhagic shock [54]. IL-6 could be released from macrophages and lymphocytes and appears to be an essential component of the inflammatory cascade that is associated with organ damage in T-H injury [51, 55].

Resveratrol has a protective role in organ damage following T-H injury via the reduction of neutrophil accumulation [46, 47, 49]. The role of resveratrol in the attenuation of lung injury is likely due to the reduction of chemokines in T-H injury [40, 42, 51]. IL-6, a critical early mediator in the lung during T-H injury, is inhibited by resveratrol treatment [42, 51]. The ability of resveratrol to modulate the expression of inflammatory cytokines, adhesion molecules, and chemokines suggests a role for resveratrol in the regulation of lung inflammation.

## 3. The Liver Protective Effect of Resveratrol in T-H Injury

The liver is considered to be a critical organ in the development of delayed organ dysfunction in patients having traumatic injuries and hemorrhagic shock [37, 39, 45, 56]. T-H injury results in massive production of proinflammatory mediators (IL-6, ICAM-1, CINC-1, and CINC-3) and the subsequent accumulation of neutrophils in the injured liver [39, 41, 47, 48]. Resveratrol reduces cytokine production and

TABLE 1: The organ-protective effects and mechanisms of resveratrol in trauma-hemorrhagic injury.

Species	Target organ	Effective dose	Effects and mechanisms	Ref.
Sprague-Dawley rat	Liver	30 mg/kg/BW	Estrogen receptor-dependent HO-1 expression↑	[20]
Sprague-Dawley rat	Liver	30 mg/kg/BW	Reduction of T-H-induced proinflammatory parameters (CINC-1↓, CINC-3↓, ICAM-1, MPO↓, and IL-6↓); Akt-dependent HO-1 expression↑	[39]
Sprague-Dawley rat	Liver	30 mg/kg/BW	Reduction of T-H-induced proinflammatory parameters (CINC-1↓, CINC-3↓, ICAM-1, MPO↓, and IL-6↓); estrogen receptor-mediated pathway	[41]
Sprague-Dawley rat	Liver	30 mg/kg/BW	Reduction of T-H-induced mitochondria damage and hepatocyte injury; increase in SIRT1 expression; and decrease in p53 and NF-κB activity; IL-6↓, MDA↓	[73]
Sprague-Dawley rat	Lung	30 mg/kg/BW	Reduction of T-H-induced proinflammatory parameters (CINC-1↓, CINC-3↓, ICAM-1, MPO↓, and IL-6↓)	[40]
Sprague-Dawley rat	Lung	30 mg/kg/BW	Estrogen receptor-dependent HO-1 expression↑	[20]
Sprague-Dawley rat	Intestine	30 mg/kg/BW	Reduction of T-H-induced proinflammatory parameters (CINC-1↓, CINC-3↓, ICAM-1, MPO↓, IL-6↓, and TNF-α↓); estrogen receptor-dependent P38/HO-1 expression↑	[18]
Sprague-Dawley rat	Heart	8 mg/kg/BW	Reduction of T-H-induced left ventricular contractility impairment through elevated SIRT1 expression; cardiac ATP↓, cytosolic cytochrome C↓, and plasma TNF-α↓	[86]
Sprague-Dawley rat	Heart	Not available	Reduction of T-H-induced mitochondria damage and improving left ventricular function through restored SIRT1 activity and PDK1 expression	[94]
Sprague-Dawley rat	Heart	30 mg/kg/BW	Reduction of T-H-induced proinflammatory parameters (ICAM-1↓, MPO↓, and IL-6↓); reduction of T-H-induced cardiac injury through elevated p-Akt activity	[38]
Sprague-Dawley rat	Endothelium	30 mg/kg/BW	Acetylcholine-induced endothelium-dependent relaxation↓ through estrogen receptor-dependent pathway; ROS radical/NADPH oxidase expression↓	[20]
Sprague-Dawley rat	Aorta	30 mg/kg/BW	NADPH-stimulated ROS↓; aortic p22phox, p47phox, gp91phox, NOX1, and NOX4 mRNA levels↓	[20]

Note: the species (Sprague-Dawley rat) are all the same in Table 1.

BW: body weight; ER: estrogen receptor; HO-1: hemeoxygenase-1; SIRT1: sirtuin 1; NF-κB: nuclear factor-kappa B; MDA: malondialdehyde; TNF-α: tumor necrosis factor-alpha; CINC-1: cytokine-induced neutrophil chemoattractant 1; ICAM-1: intercellular adhesion molecule 1; MPO: myeloperoxidase; IL-6: interleukin 6; ROS: reactive oxygen species; NOX: NADPH oxidase; PDK1: pyruvate dehydrogenase kinase 1.

neutrophil accumulation in a rodent model of LPS-induced hepatic oxidative stress and inflammation [57].

Resveratrol binds to ER-α and ER-β and therefore alters the transcriptional activity of estrogen-responsive target genes [17, 19, 58, 59]. Resveratrol could modulate TNF-α

genes expression and suppress IL-6 transcription via an ER-α signal integration [16]. Other studies demonstrated the role of sexual dimorphism in response to injury and showed the importance of sex steroids on the maintenance of organ function in T-H injury [45, 47, 60, 61]. The administration of

resveratrol in combination with an ER antagonist ICI 182,780 blocks the hepatoprotective effect and such ER pathway is critical in hepatoprotection in T-H injury [41]. Building on these findings, ER pathways may be potentially useful therapies in the treatment of trauma patients [41, 62, 63]. In addition, estrogen treatment upregulates phosphatidylinositol 3-kinase (PI3K)/Akt expression via an estrogen receptor following T-H injury [64].

HO-1, a stress-inducible heme-degrading enzyme, provides cytoprotection against oxidative stress and inflammatory reaction [65, 66]. HO-1 expression is upregulated during T-H injury, and its induction appears to play a central role in the preservation of organ microcirculation under such conditions [67, 68]. A growing body of evidence demonstrates that Akt activation induces HO-1, which is known to have a protective effect in many organs under various deleterious conditions, including T-H injury [39, 42, 68, 69]. The upregulation of HO-1 causes a reduction of chemokines, cytokines, and adhesion molecules. It also decreases neutrophil accumulation and ameliorates organ injury in trauma-related shock status [39, 42, 70]. The administration of  $17\beta$ -estradiol or flutamide (an antiandrogen drug) in T-H injury increases HO-1 expression, which attenuates the organs' dysfunction and injury [67–69]. The PI3K/Akt is an important signaling pathway controlling endogenous negative feedback or compensatory mechanism, in which proinflammation and chemotactic events are limited in response to injury [37, 39, 64]. Activation of PI3K/Akt signaling cascade by resveratrol has been observed in different tissues [38, 39, 71, 72]. Resveratrol-mediated increase in HO-1 is found to be Akt-dependent. When resveratrol is coadministered with PI3K/Akt antagonist, it abolishes the resveratrol-mediated HO-1 increase and hepatic protective effects in T-H injury [39, 70]. These results indicate that resveratrol attenuated liver damage and decreased proinflammatory mediator expression in T-H injury, likely through Akt-dependent HO-1 pathway [39, 70].

In addition, Powell et al. demonstrated that resveratrol could reduce T-H injury-induced mitochondria damage and hepatocyte injury. Resveratrol illustrates a protective effect through an increase in SIRT1 expression and a decrease in p53 and NF- $\kappa$ B activity. It also inhibits proinflammatory mediator IL-6 and lipoperoxidation MDA expression [73].

#### 4. The Intestinal Protective Effect of Resveratrol in T-H Injury

Intestinal tract is highly sensitive to injury. T-H injury could induce oxidants release, leading to microvascular permeability change, interstitial edema, mucosal barrier dysfunction, and inflammatory cell infiltration. ER also plays a pivotal role in intestinal injury after T-H shock. Previous reports showed that ER leads to the induction of p38 MAPK [18, 47, 74, 75], which contributes to the protection of cell/tissue in response to a variety of stimuli [76–78]. Estrogen-mediated anti-inflammatory and organ-protective effects are abolished by the administration of a p38 MAPK inhibitor SB-203580 following T-H injury [18, 75].

p38 MAPK activation regulates mucosal recovery in ischemic-injured porcine ileum [79] and protects glomerular epithelial cells against complement-mediated cell injury [80]. The p38 MAPK phosphorylation contributes to intestine-protection in T-H injury after ischemic preconditioning or T-H [18, 47, 74, 75]. Resveratrol also reduces chronic colonic inflammation [81] and protects  $H_2O_2$ -treated embryonic rat heart H9c2 cells via the p38 MAPK pathway [82].

The upregulation of HO-1 is known for its protective role in cellular stress during inflammation, ischemia, and radiation, as well as the anti-inflammatory and antiapoptotic effects. Resveratrol protects the intestinal epithelial barrier function against TNF- $\alpha$  and oxidative stress through upregulation of HO-1 expression in intestinal ischemia/reperfusion injury [83]. p38 MAPK activation induces HO-1 expression and maintains organ function under various stresses and injuries. Recent studies indicate that the treatment of animals with SB-203580, which blocks p38 MAPK, abolishes resveratrol-induced upregulation of HO-1 after T-H [18, 75]. These findings indicate that the salutary effects of resveratrol-mediated attenuation of intestinal injury in T-H are mediated, at least in part, through ER-dependent p38 MAPK/HO-1 upregulation.

#### 5. The Cardioprotective Effect of Resveratrol in T-H Injury

Resveratrol has been shown to possess cardioprotective effects during ischemia-reperfusion injury [84, 85] and decreases organ injury in T-H injury [38, 86]. Cardiac injury is associated with increased neutrophil accumulation [38, 47] and such in small intestine is correlated with the attenuation of trauma-hemorrhage-induced cardiac dysfunction [18].

Activation of the PI3K pathway protects cells or organs against hypoxia and ischemia-reperfusion injury via inhibition of the apoptosis machinery [87, 88]. Modulation of the PI3K/Akt pathway with the PI3K inhibitor wortmannin suppresses coagulation and inflammation and decreases the survival of mice subjected to sepsis [89]. PI3K/Akt pathway also mediates neutrophils activation and regulates leukocyte signaling and function, to undergo chemotaxis [90]. Resveratrol decreases the production of proinflammatory mediators and ameliorates cardiac injury in T-H injury [38]. Blockade of Akt activation abolishes the salutary effects of resveratrol in the heart following T-H [38]. Altogether, resveratrol-related cardioprotective effect is likely mediated through an Akt-dependent pathway in T-H injury [38].

SIRT1 has been shown to regulate the mammalian genes transcription and silence the tumor suppressor genes [91, 92]. The SIRT1 transcription-modulating proteins demonstrate a fine balance in response to intracellular stimulus, such as hypoxia or stress signals. The beneficial effects of resveratrol mediated by SIRT1 activation can be contributed by different organs [24, 86, 93, 94]. Resveratrol improves heart function following T-H injury by downregulating SIRT1 expression [86]. The protective effect of resveratrol on left ventricular contractility and systemic TNF- $\alpha$  levels is abolished by sirtinol (a SIRT1 inhibitor) [86]. In addition, Jian et al.



indicated that SIRT1 enzyme activity is decreased following T-H injury [94]. SIRT1 modulates left ventricular function in T-H injury through regulation of cellular energetic. The results suggest that the reduced SIRT1 levels in T-H injury may be related to declining mitochondrial function [94].

## 6. The Endothelial Protective Effect of Resveratrol in T-H Injury

Oxidative stress and superoxide radical generation are believed to contribute to the pathogenesis of endothelial dysfunction in low-flow states [95–97], resulting in inadequate tissue perfusion [96, 97].

Endothelial nicotinamide adenine dinucleotide phosphate-oxidase (NOX) is an important source of reactive oxygen species (ROS) of the vasculature, and, under various stressful conditions, a significant increase in NOX-generated ROS by the endothelium has been observed [95, 98]. Elevated ROS is a critical contributing factor to endothelial dysfunction, and antioxidants have been demonstrated to reduce ROS-induced injuries [95, 98]. Resveratrol has broad antioxidant and anti-inflammatory activities in a number of biological reactions [15, 99, 100], for instance, cardiovascular beneficial effects on atherosclerosis, ventricular arrhythmia, and myocardial ischemia-reperfusion I/R injury [101, 102]. Resveratrol's cardioprotective effects in I/R injury are achieved through its ROS-scavenging activity [77, 103]. However, the cardiovascular benefit of resveratrol may not simply be attributable to its antioxidant effect. Recent findings show that resveratrol reduces NOX activity in rat aortic endothelial cells and macrophages [20, 104, 105]. Resveratrol prevents T-H injury-induced oxidative stress and protects endothelium from subsequent oxidative functional damages [20]. The beneficial effects include inhibition of the NOX activity and direct scavenging of ROS. The protective effects of resveratrol are likely through suppression of the NOX enzyme complex activity in the cell membrane and the cytosol, including decreased membrane-bound proteins p22phox and gp91phox and cytosolic protein p47phox [20].

HO-1 appears to act as a protective agent in many organs against insults, such as trauma, ischemia, and oxidative stress [67, 106, 107]. Estrogen or flutamide enhances HO-1 expression, and resveratrol can modulate HO-1 induction via ER-related pathway [18, 20]. The upregulation in HO-1 is associated with the prevention of endothelial dysfunction and the salutary effects of resveratrol on endothelial function are mediated in part by upregulation of the HO-1-related pathway via ER [20].

## 7. Conclusions

Resveratrol has been shown to possess the beneficial effects in various studies and experimental conditions. There is increasing evidence that resveratrol maintains organ function after trauma or shock-like states. Resveratrol can attenuate organs injury in T-H injury through multiple pathways. However, the protective benefits of resveratrol may not simply be attributed to its anti-inflammatory or antioxidant effect.

It is implicated that resveratrol is also mediated in part via a variety of intracellular signaling pathways, including the regulation of the HO-1/MAPK, PI3K/Akt, ER, and SIRT1. This complex network needs additional elucidation in future experimental studies and clinical trials.

## Abbreviations

T-H:	Trauma-hemorrhage
ER:	Estrogen receptor
SIRT1:	Sirtuin 1
HO-1:	Hemeoxygenase-1
p38 MAPK:	p38 mitogen-activated protein kinase
PI3K:	Phosphatidylinositol 3-kinase
Akt:	Protein kinase B
NF- $\kappa$ B:	Nuclear factor-kappa B
ROS:	Reactive oxygen species
MDA:	Malondialdehyde
NOX:	NADPH oxidase
MPO:	Myeloperoxidase
CINC-1:	Cytokine-induced neutrophil chemoattractant 1
ICAM-1:	Intercellular adhesion molecule 1
IL-6:	Interleukin 6
TNF- $\alpha$ :	Tumor necrosis factor-alpha
PDK1:	Pyruvate dehydrogenase kinase 1.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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