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Red wine extract, resveratrol, on maintenance of organ function following trauma-hemorrhage

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Running Title: Role of red wine extract following injury

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ABSTRACT:

Resveratrol, is a polyphenol that can be extracted from grapes and red wine, possess potential anti-inflammatory effects, which would result in the reduction of cytokine production, the alteration of the expression of adhesion molecule molecules, and the inhibition of neutrophil function. Resveratrol might also act as an antioxidant, anti-aging, and control of cell cycle and apoptosis. Resveratrol has been shown to have protective effects for patients in shock-like states. Such protective phenomenon is reported to be implicated in a variety of intracellular signaling pathways including the regulation of the mitogen-activated protein kinases (MAPK)/ hemeoxygenase-1 (HO-1) pathway, activates estrogen receptor (ER), and the mediation of pro-inflammatory cytokines, reactive oxygen species (ROS) formation and reactive. Moreover, through anti-inflammatory effects and antioxidant properties, the resveratrol is believed to maintain organ function following trauma-hemorrhage.

Key words: resveratrol, anti-inflammatory, trauma-hemorrhage.

INTRODUCTION:

Resveratrol is a naturally occurring plant antibiotic known as phytoalexins, found in many

plants, nuts, and fruits, and is abundant in grapes and red wine [1,2]. Several recent reports have shown the protective effects of resveratrol in different pathological models and experimental conditions [3-7]. Many clinical researchers also indicate the beneficial effects of resveratrol in various human diseases [8-13]. A growing body of evidence indicates that resveratrol may play potential therapeutic roles in human health by its various beneficial biological effects, e.g., anti-inflammation, anti-aging, antioxidant, anti-diabetes, and apoptosis [10,14-17]. A number of target molecules mediating the above mentioned protective effects of resveratrol have been identified, including the AMP-activated protein kinase (AMPK), the Akt kinase, the estrogen receptors (ER), the adenosine receptor, the cyclooxygenase-1 (COX-1), the histone/protein deacetylase sirtuin 1 (SIRT1), the nuclear factor-E2- related factor-2 (Nfr2), and Nuclear Factor-Kappa B (NF-kB) [1,18]. A variety of laboratory and clinical studies also indicate that resveratrol may lead to organ and tissue protective effects against various injuries [20-26]. Ischemic/reperfusion injury induces free radical formation and inflammation within hours and results in the excessive production of pro-inflammatory mediators that play a significant role in the development of multiple organ dysfunctions under those conditions [27,28]. Specifically, resveratrol has been suggested as a therapeutic agent to treat shock-like and ischemic states due to its anti-oxidative and anti-inflammatory activities [29-35]. In this review, we summarize the protective pathways of resveratrol with emphasis on maintenance of organ function following trauma-hemorrhage (T-H) (Table 1).

The protective effect of resveratrol on lung following T-H

Trauma-hemorrhage results in excessive production of pro-inflammatory mediators, such as cytokines and chemokines. The enhanced secretion of pro-inflammatory cytokines is an important factor in the initiation and perpetuation of organ injury [29,36,37]. These cytokines recruit other immune cells including neutrophils, thereby increasing leukocyte trafficking and organ injury [38-40]. Neutrophils can release mediators which diffuse across the endothelium and injure parenchymal cells [38,40]. In addition, neutrophils can leave the microcirculation and migrate to matrix proteins or other cells [29,38,40]. Studies have shown that neutrophils are activated following T-H [39,40] and that lung injury is associated with an increased neutrophil accumulation in the lung after T-H [29,41]. Studies have been reported that reduction of neutrophil accumulation is shown to play a protective role in organ damage after T-H [27,29,36]. The activated neutrophils appear to infiltrate the injured lung in parallel with increased expression of adhesion molecules on endothelial cells and result in elevated local chemokines/cytokines levels following hemorrhagic shock [29,40,42]. The intercellular

adhesion molecule (ICAM)-1 enhances firm adhesion of neutrophils to the vascular endothelium and is markedly up-regulated after T-H [40,43,44]. Furthermore, trauma-hemorrhagic shock increases ICAM-1 levels in the lung [29,40,45]. Chemokines, such as cytokine-induced neutrophil chemoattractant (CINC)-1 and CINC-3, are potent chemoattractants for neutrophils. Moreover, the levels of the chemokines, CINC-1 and CINC-3, are elevated in the lung after T-H. Studies have also indicated that overproduction of those chemokines leads to lung injury after T-H [29.45].

Table 1. Protective effects and mechanisms of the resveratrol on different organs following trauma-hemorrhage

Species/Targets	**Effective dose**	**Effects and mechanisms**	**Ref.**
Sprague-Dawley rat/Lung	30 mg/kg of body weight	Reduction of T-H-induced proinflammatory parameters (MPO↓,CINC-1↓, CINC-3↓,ICAM-1, and IL-6↓)	[29]
Sprague-Dawley rat/Lung	30 mg/kg of body weight	HO-1↑(estrogen receptor-dependent) expression	[37]
Sprague-Dawley rat/Liver	30 mg/kg of body weight	HO-1↑(estrogen receptor-dependent) expression	[37]
Sprague-Dawley rat/Liver	30 mg/kg of body weight	Akt-dependent HO-1 expression↑; Proinflammatory parameters ↓ (MPO↓,CINC-1↓, CINC-3↓,ICAM-1, and IL-6↓)	[36]
Sprague-Dawley rat/Liver	30 mg/kg of body weight	ER-related pathway; Proinflammatory parameters ↓ (MPO↓,CINC-1↓, CINC-3↓,ICAM-1, and IL-6↓)	[28]
Sprague-Dawley rat/Intestine	30 mg/kg of body weight	P38/HO-1 expression↑ (estrogen receptor-dependent); Proinflammatory parameters ↓(MPO↓,CINC-1↓, CINC-3↓,ICAM-1, IL-6↓ and TNF-α↓)	[22]
Sprague-Dawley rat/Heart	8 mg/kg of body weight	Reduction of T-H-induced cardiac c-Myc ↑and Pgc-1↑ (SIRT1-dependent); Cardiac ATP↓, cytosolic cytochrome C↓, TNF-α↓	[89]
Sprague-Dawley rat/Heart	30 mg/kg of body weight	Restores T-H-induced cardiac p-Akt.activity ↑; Proinflammatory parameters ↓ (MPO↓,IL-6↓ and ICAM-1↓)	[27]
Sprague-Dawley rat/Endothelium	30 mg/kg of body weight	Acetylcholine-induced endothelium-dependent relaxation↓ (estrogen receptor-dependent); ROS radical/NADPH oxidase expression↓	[37]
Sprague-Dawley rat/Aorta	30 mg/kg of body weight	NADPH-stimulated ROS↓; Aortic p22phox, p47phox, gp91phox, NOX1 and NOX4 mRNA levels↓	[37]
Wistar rat/Arterial smooth muscle cells	15 mg/kg of body weight	Inhibit TH-induced mitochondrial membrane potential and intracellular ATP decrease	[100]

Furthermore, there is convincing evidence that interleukin (IL)-6 plays a significant role on organ injuries and is required for expression of adhesion molecules and release of chemokines [46,47]. IL-6 also appears to be an essential component of the inflammatory cascade that is associated with lung injury in hemorrhagic shock [29,45]. Moreover, IL-6-deficient mice shows less neutrophil infiltration and organ damage as compared with wild-type mice under those conditions [47,48]. The cytokines are important early mediators in the lung during T-H, and are required for expression of adhesion molecules and chemokines [49,50]. The ability of resveratrol to modulate expression of inflammatory cytokines as well as adhesion molecules and chemokines suggests a role for resveratrol in the regulation of lung inflammation.

The protective effect of resveratrol in the liver following T-H

The liver is considered to be a critical organ in the development of delayed organ dysfunction in patients having traumatic injuries and hemorrhagic shock [40,51,52]. T-H results in excessive production of pro-inflammatory mediators, and the subsequent accumulation of neutrophils in the liver is associated with hepatic injury [36,43,52]. Resveratrol reduces neutrophil and cytokine production in vivo in a rodent model of LPS-induced airway inflammation [53,54]. Previous studies have shown that resveratrol binds and increases the transcriptional activity of estrogen receptor (ER)-α and ER-β [55]. Previous studies have made contributions in exploring the role of sexual dimorphism and response to injury and demonstrated the importance of sex steroids on the maintenance of organ function after T-H [40,52,56]. Previous studies have also shown that resveratrol binds to ER and activates the transcription of estrogen-responsive target genes [57]. Our previous studies showed that administration of resveratrol in combination with an ER antagonist ICI 182,780 blocked the hepatoprotective effect and demonstrated that ER pathways are critical to the mechanism of resveratrol induced post-resuscitation hepatoprotection [28]. Building on these concepts, ER pathways may be critical to the use of potential therapies in the treatment of trauma patients [28,49].

Previous studies have also shown that estrogen administration after T-H up-regulates phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) expression via an estrogen receptor [58]. The PI3K/Akt is known to be an endogenous negative feedback or compensatory mechanism, which serves to limit pro-inflammatory and chemotactic events in response to injury [59,60]. In addition, PI3K/Akt pathway is known to play a pivotal role in the ability of neutrophils to undergo chemotaxis [61-63]. Previous studies have shown that hemeoxygenase 1 (HO-1) expression is up-regulated after hemorrhagic shock, and that its

induction seems to play a central role in the preservation of organ microcirculation under such conditions [64]. A growing body of evidence indicates that Akt activation induces HO-1, which is known to play a protective role in many organs under various deleterious conditions, including T-H [64,65]. Up-regulation of HO-1 causes a reduction of cytokines, adhesion molecules, chemokines, and neutrophil accumulation, and ameliorates organ injury in shock status [37,43,45,64]. Studies have also shown that administration of 17β-estradiol or flutamide after T-H increase HO-1 expression, which prevents the organs from dysfunction and injury [22,65,66]. Resveratrol-mediated increase in HO-1 is found to be Akt-dependent, because co-administration of HO antagonist with resveratrol abolished the increase in HO-1 and the salutary effects of resveratrol in the liver following T-H [43]. Activation of PI3K/Akt signaling cascade by resveratrol has been observed in different tissues [30,67-69]. These results indicate that resveratrol administration after T-H decreases pro-inflammatory mediator levels and attenuates liver damage, likely through Akt-mediated up-regulation of HO-1 [36,43].

The protective effect of resveratrol in the intestine following T-H

Estrogen receptor is also reported to play an important role in intestinal injury after T-H. The p38 mitogen activated protein kinase (MAPK) has been reported to regulate inflammatory response after T-H [22,70-72]. An increasing body of evidence shows that ERs lead to the induction of p38 MAPK [22,70,73]. Estrogen-mediated attenuation of the inflammatory response to shock-induced organ injury is abolished by the presence of a p38 MAPK inhibitor SB-203580 [22,70,72]. A growing body of evidence indicates that p38 MAPK activation induces HO-1, which is known to play a protective role in many organs under various deleterious conditions, including T-H [22,70]. Up-regulation of HO-1 causes a reduction of pro-inflammatory mediators, cytokines/chemokines and adhesion molecules, along with neutrophil accumulation and amelioration of organ injury in shock status [41,45,74]. A number of studies have shown that p38 MAPK activation contributes to the protection of cell/tissue responses to a variety of stimuli [75-77]. P38 MAPK phosphorylation is also reported to be intestine-protective after ischemic preconditioning or T-H [22,70,78]. Studies have also indicated that p38 MAPK activation regulates mucosal recovery in ischemic-injured porcine ileum [79] and protects glomerular epithelial cells against complement-mediated cell injury [80]. It suggests that the salutary effects of resveratrol are mediated by p38 MAPK-dependent HO-1 upregulation. Our recent study showed that treatment of animals with SB-203580, which blocks p38 MAPK, abolished resveratrol-induced up-regulation of HO-1 after T-H [22]. These findings indicate that the

salutary effects of resveratrol are mediated in part through ER-dependent p38 MAPK/HO-1 upregulation.

The protective effect of resveratrol in the heart following T-H

Resveratrol has been shown to have cardioprotective effects during ischemia reperfusion [81], and previous studies have shown that resveratrol can attenuate organ injury after T-H [27,36]. Activation of the PI3K pathway protects organs or cells against ischemia-reperfusion injury and hypoxia through suppression of the apoptosis machinery [82,83]. Inhibition of the PI3K/Akt pathway with the PI3K inhibitor wortmannin increases serum cytokine levels and decreases the survival of mice subjected to sepsis [60,84]. PI3K/Akt pathway is known to play a pivotal role in the ability of neutrophils to undergo chemotaxis [64,85]. Studies have demonstrated that cardiac injury is associated with increased neutrophil accumulation [40,86] and our previous studies have also shown that reduction of neutrophil accumulation after hemorrhagic shock in small intestine correlated with the improvement of cardiac function [22]. Resveratrol has been shown to ameliorate cardiac injury and production of pro-inflammatory mediators after T-H [27]. Blockade of Akt activation abolishes the salutary effects of resveratrol in the heart following T-H [27]. These findings provide evidence that resveratrol-mediated cardioprotection is likely mediated via an Akt-dependent pathway after T-H [27].

Sirt1 (Sirtuin 1) has been shown to regulate mammalian genes transcription and silence tumor suppressor genes [87,88]. The Sirt1 transcription-modulating proteins also showed a fine balance in response to intracellular cues, such as hypoxia or stress signals. The beneficial effects of resveratrol mediated by Sirt1 activation can be contributed by different organs [4,89-91]. Studies have shown that resveratrol improves cardiac function following T-H by modulating Sirt1 [89]. Resveratrol could abrogate the T-H-induced down-regulation of Sirt1 expression and most of the effect abolished by sirtinol (a Sirt1 inhibitor). The salutary effect of resveratrol on left ventricular contractility and systemic TNF-α levels was abolished by sirtinol [89].

The protective effect of resveratrol on endothelium following T-H

Previous studies have shown that vascular endothelial cell dysfunction leading to inadequate tissue perfusion which occurs after hemorrhagic shock and persists despite fluid resuscitation [92,93]. Oxidative stress and superoxide radical generation are believed to contribute to the pathogenesis of endothelial dysfunction in low-flow states [66,93,94]. Endothelial nicotinamide adenine dinucleotide phosphate-oxidase (NOX) is a major source of reactive

oxygen species (ROS) of the vasculature, and previous studies have shown that there was a marked increase in NOX-generated ROS by the endothelium under stressful conditions [66,94]. Elevated ROS is considered a major contributing factor to endothelial dysfunction, and anti-oxidants have been found to attenuate ROS-induced injuries [66,94]. Resveratrol has been shown to have broad anti-oxidant activities in a number of biological systems [95,96]. Resveratrol has been demostrated to have cardioprotective effects during ischemia-reperfusion through its ROS-scavenging activity [81]. However, the cardiovascular benefit of resveratrol may not simply be attributable to its anti-oxidant effect, and recent findings indicate that resveratrol reduces NOX activity in rat aortic homogenate and macrophages [97]. The NOX complex in phagocytic cells is a flavocytochrome composed of two membrane bound proteins, gp91phox and p22phox, and a cytosolic protein, p47phox [98]. Our recent studies have shown that resveratrol prevents T-H-elicited oxidative stress and protects endothelium from subsequent functional damages [94]. The beneficial effects include suppression of the NOX activity and direct scavenging of ROS. The inhibitory effect of resveratrol on the NOX activity appears to be mediated through influence of the active NOX enzyme complex assembly in the cell membrane and the cytosol, as is evidenced from reduced membrane-bound proteins p22phox and gp91phox and cytosolic protein p47phox [37,94]. Furthermore, the recent study has shown that resveratrol could reduce mitochondrial dysfunction and lysosomal stability of rat's arteriolar smooth muscle cells (ASMCs) following T-H [99].

HO-1 appears to act as a protective agent in many organs against insults, such as ischemia and oxidative stress [65,100]. Resveratrol can modulate HO-1 induction and previous studies also have shown that estrogen or flutamide enhances HO-1 expression via ER [22,36]. Our recent studies suggest that up-regulation in HO-1 was associated with prevention of endothelial dysfunction and the salutary effects of resveratrol on endothelial function are mediated in part by up-regulation of the HO-1- related pathway via ER [94].

CONCLUSIONS:

Resveratrol has been shown to have 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 following T-H through multiple pathways. However, the protective benefits of resveratrol may not simply be attributed to its anti-inflammatory or anti-oxidant 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 (Figure 1). This complex network needs

additional elucidation in future experimental studies and clinical trials.

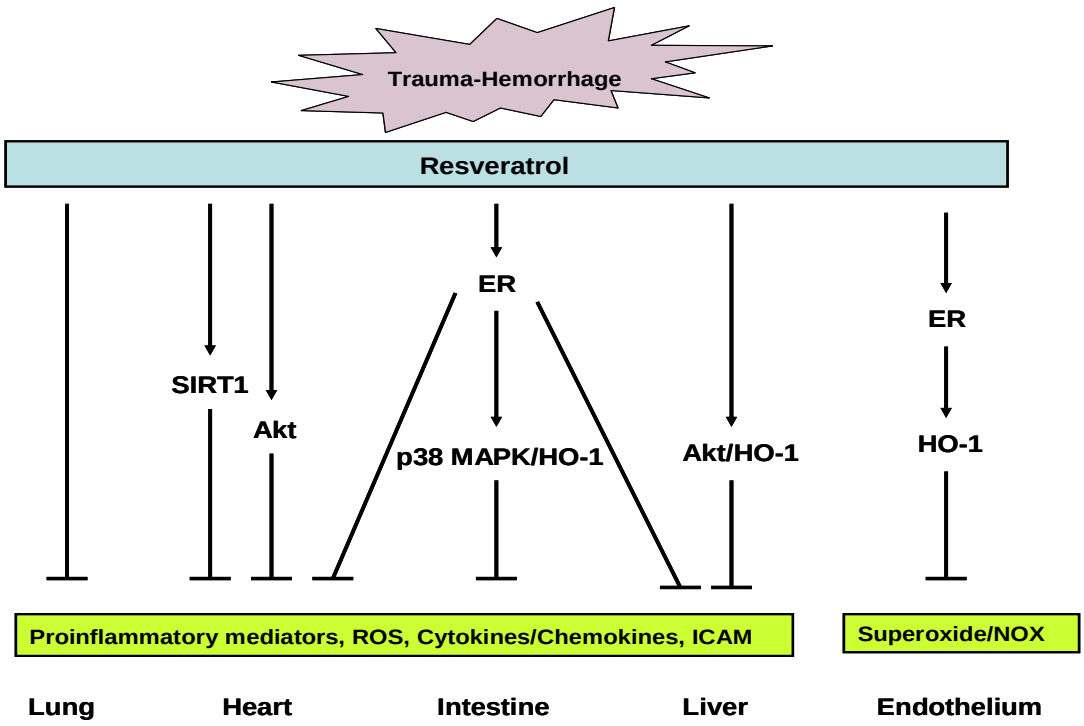

Figure 1. The pathways of resveratrol on maintenance of organ function following trauma-hemorrhage. ER, estrogen receptor; SIRT1, sirtuin 1; HO-1, hemeoxygenase 1; ROS, reactive oxygen species; ICAM, intercellular adhesion molecule; NOX, NADPH oxidase.

Abbreviations: Trauma-Hemorrhage (T-H), Estrogen Receptor (ER), Reactive Oxygen Species (ROS), Hemeoxygenase-1 (HO-1), Nuclear factor-E2- related factor-2 (Nfr2), Nuclear Factor-Kappa B (NF-kB), Phosphatidylinositol 3-kinase (PI3K), Protein Kinase B (Akt), Mitogen-Activated Protein Kinase (MAPK), Cyclooxygenase-1 (COX-1), Sirtuin 1 (SIRT1), Nicotinamide adenine dinucleotide phosphate-oxidase (NOX),

Competing interests: The authors declare that they have no competing interests.

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