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Determination of malondialdehyde, raftlin, and sphingosine 1-phosphate levels in hepatic ischemia-reperfusion injury in rats

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Hepatic ischemia–reperfusion (HIR) injury involves inflammation and oxidative stress resulting from paradoxical cellular stress upon reperfusion. This study investigated the protective effects of resveratrol (RSV) against HIR injury using oxidative stress, inflammation, and cellular signaling biomarkers. Twenty-eight male Wistar albino rats were randomly divided into four groups: Control, HIR (30 min ischemia + 30 min reperfusion), Vehicle (HIR + 0.9% NaCl 100 mg/kg/day), and RSV (50 mg/kg/day) administered three days prior to the procedure. Liver tissues were analyzed for malondialdehyde (MDA), raftlin, sphingosine-1-phosphate (S1P) levels, and histopathological assessments. Statistical analyses employed Kruskal-Wallis and Mann-Whitney U tests (P<0.05). MDA and raftlin levels were highest, and S1P levels lowest, in the HIR group (P<0.001). RSV significantly attenuated HIR-induced biochemical changes compared to HIR and vehicle (P<0.05). Histopathologically, RSV reduced vascular congestion and inflammation while preserving cellular architecture. This study is the first to demonstrate RSV's protective potential against HIR injury via modulation of oxidative stress, inflammation, and cellular signaling. Additionally, raftlin was identified as a potential biomarker for inflammation in HIR, highlighting its relevance for future research. These findings provide novel insights into the mechanisms of HIR injury and suggest RSV as a candidate for further preclinical investigation.

Keywords: oxidative stress, inflammation, cellular signaling, resveratrol

Introduction

Ischemia/reperfusion (I/R) injury is a multifactorial process that can exert effects on molecular and cellular mechanisms. In ischemic conditions, the lack of oxygen in cells reduces ATP synthesis, lowers intracellular pH, and disrupts the function of ion pumps, leading to the accumulation of intracellular Ca^{2+} [1]. Subsequently, the sudden reoxygenation accompanying reperfusion triggers the production of reactive oxygen species (ROS). Following I/R, numerous pathological processes develop, including cellular injuries such as necrosis, apoptosis, and ferroptosis, as well as oxidative stress, inflammation, blood-brain barrier disruption, and fibrosis[2].

Oxidative stress exhibits profound effects on the pathological mechanisms during both the early and late phases of Hepatic Ischemia-Reperfusion (HIR) injury. The nutrient depletion and hypoxic conditions characteristic of the HIR period increase xanthine oxidase activation within hepatocytes and sinusoidal endothelial cells. Furthermore, Kupffer cells enhance the production of ROS, thereby triggering lipid peroxidation and ensuing cellular damage[3]. Lipid peroxidation disrupts cell membrane integrity, leading to structural and functional losses. Increased oxidative stress triggers inflammation in Kupffer cells, resulting in elevated levels of aldehyde-derived products such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), which serve as markers of ROS and lipid peroxidation[3,4] . MDA, whose levels have been found to be elevated in various diseases in numerous publications, was evaluated as an indicator of HIR-induced oxidative damage in this study.

One of the important biochemical mechanisms of I/R injury is the strong activation of the inflammatory response. Prolonged ischemia causes the release of damage-associated molecular patterns (DAMPs) due to cellular damage, followed by an increase in pro-inflammatory cytokine levels. During the reperfusion phase, endothelial activation and cytokine release trigger neutrophil infiltration, further aggravating tissue damage[5]. Raftlin, one of the parameters in our study, is an important membrane protein found in

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lipid rafts that plays an important role in immune response and cell signaling. Recent studies have shown it to be a potent marker of cellular inflammation[6].

Sphingosine-1-phosphate (S1P), one of the important bioactive products of sphingolipid metabolism, has the capacity to regulate various cellular processes beyond cell membrane structure[7].

During HIR injury, it has been reported that an increase in S1P levels enhances endothelial barrier function and reduces vascular permeability[8]. Additionally, S1P reduces cell death by suppressing apoptosis in hepatocytes and modulates the inflammatory response that occurs during the reperfusion process[9]. Given these characteristics, it is thought that S1P plays a protective role in liver tissue by reducing the effects of both oxidative stress and inflammation in I/R injury. Therefore, our study is designed to investigate the effects of HIR and resveratrol administration on S1P levels.

Antioxidants play a role in reducing the effects of oxidative stress. Resveratrol, which is employed in the present study, is a natural phytoalexin found in many different plants, most notably in grapes[10,11]. Resveratrol, which has antioxidant and anti-inflammatory properties, exerts these effects by activating the SIRT-1/NF-κB (silent information regulator-1 / nuclear factor kappa B) signaling pathway[12].

I/R injury, also known as the oxygen paradox, can lead to multiple organ failure by causing damage not only to the primary ischemic organ (such as the liver, brain, kidney, or heart) but also triggering systemic damage in distant non-ischemic tissues. The literature exhibits a critical void in studies that jointly evaluate oxidative stress (MDA), inflammation, and lipid raft relationships (Raftlin) in HIR damage, as well as S1P levels from cellular signaling lipid mediators. Furthermore, the lack in publications showing the protective effects of resveratrol on these parameters in the HIR model highlights the novelty of our study and underscores its potential to provide significant contributions to the literature.

Materials and Methods

This study has been approved by the Kahramanmaras Sutcu Imam University Faculty of Medicine Local Animal Ethics Committee (KSUTIP-HADYEK) (Date: 02/27/2025 Approval number: 01). All experimental protocols were conducted in accordance with the standards of KSUTIP-HADYEK and the European Union's 2010/63/EU directive on laboratory animal welfare.

Study Design

According to the G*Power analysis (version 3.1), which was conducted with a power of 0.80, an effect size of 0.7, and an alpha error probability of 0.05, it was determined that each group should include at least six animals. In this study, a total of 28 male Wistar albino rats weighing 220–300 g at 8–10 weeks of age were used (Kahramanmaras Sutcu Imam University Faculty of Medicine Experimental Research Laboratory, Kahramanmaras). The rats were kept at a humidity level of 50–60% and a room temperature of 22±1°C, with a light cycle of 12 hours of light and 12 hours of darkness. The rats were fed a basal diet throughout the study period.

Subjects were randomly divided into four groups: control group (n=7), hepatic ischemia/reperfusion (HIR) group (n=7), vehicle group (n=7), and resveratrol (treatment) group (n=7). The samples were subjected to the experiment for 4 days. On the morning of the 5th day, ketamine hydrochloride (Ketalar vial, Eczacıbası/Turkiye) (50mg/kg) was administrated intramuscularly. The hepatic tissues taken for the study were washed with 0.9% NaCl and stored at -80°C (Haier Bio-Medical Ultra Low Temperature Freezer, China) until biochemical analyses.

Control Group (n=7)

No intervention was performed, and at the end of the experiment, after anesthetic administration, the abdominal region of the rats was opened and their hepatic tissues were obtained.

HIR Group (n=7)

Subjects were fasted for 12 hours prior to ischemia. Under anesthesia, the subjects underwent laparotomy via a midline incision. After freeing the hepatic pedicle, a silicone-padded atraumatic clamp was applied to the hepatic artery, portal vein, and bile duct for 30 minutes to achieve total hepatic ischemia, followed by 30 minutes of reperfusion after ischemia.

Vehicle (HIR+ NaCl) Group (n=7)

This group received 0.9% NaCl (100 mg/kg/day) intraperitoneally for 3 days prior to surgery. After anesthesia, the abdominal region was opened and hepatic I/R was applied to the subjects for 30 minutes, after which the subjects' hepatic tissues were removed.

Resveratrol (RSV) Group (n=7)

The pharmacologically active and stable isomer trans-resveratrol was obtained in purified form from Sigma (St. Louis, MO, USA; 500 mg) and dissolved in a 0.9% NaCl solution according to the manufacturer's instructions. RSV (50 mg/kg/day) was administered intraperitoneally to this group 3 days prior to I/R. After the third day, there was a one day waiting period, followed by 30-minute I/R sessions, after which the hepatic tissues of the subjects were collected, and the experiment was terminated.

Biochemical Analyses

Homogenization of Hepatic Tissues

The hepatic tissues of the subjects were homogenized in an ice-cold environment using a homogenizer (ika t18 basic ultra turrax homogenizer, Germany) with 1.15% KCl (1:10 ratio). The homogenates were then centrifuged at 14.000 rpm for 30 min (Hettich Zentrifugen Rotanta 460R, Germany) to obtain the supernatant. Protein, raftlin, MDA, and S1P levels were measured in the supernatants. The Lowry method was used for total protein measurement[13].

MDA Level Determination

MDA levels were measured spectrophotometrically according to the thiobarbituric acid (TBA) method[14].

Determination of Raftlin and S1P Levels

Rat RFTN1 (Raftlin) (MyBioSource Company, USA Cat number: MBS2533590) and Rat S1P (MyBioSource Company, USA Cat number: MBS1600586) were measured at 450 nm using a microplate reader (Organon Teknika Microwell System Reader 230S, Germany) in accordance with the manufacturer's recommendations.

Histopathological Analyses

For histopathological assessment, the liver tissues were fixed in 10% buffered neutral formalin for 48 hours. The fixed tissues were subsequently dehydrated using ascending alcohol series (70%, 80%, 90%, 96%, and 100%). Following dehydration, a clearing process was conducted where the tissue samples were passed through xylene and then embedded in paraffin to obtain paraffin blocks. For hematoxylin-eosin staining, 5 µm thick sections were taken from the paraffin blocks. After deparaffinization, the sections were rehydrated using graded alcohol series (100%, 96%, 80%). Sections stained with hematoxylin-eosin (H&E) were covered with entellan and examined under a light microscope. Sections obtained from each group (n=7) were evaluated for the presence of vascular congestion, sinusoidal dilatation, mononuclear cell infiltration, vacuolation in hepatocytes, and necrosis.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics 22.0 software. Given the small sample size (n=7), non-parametric tests were employed with data presented as median (minimum–maximum range). Two group comparisons were conducted using a Mann-Whitney U test, while a Kruskal-Wallis test was used for multiple group comparisons. For all analyses, $P<0.05$ was considered significant.

Results

Biochemical Analyses

The four groups in our study (control, HIR, Vehicle, and RSV) were compared in terms of MDA, raftlin, and S1P levels. According to our findings, MDA and raftlin levels were highest in the HIR group, while S1P levels were lowest among those groups ($P<0.001$) (Table 1) (Fig 1).

Pairwise comparisons revealed statistically significant differences in MDA, raftlin, and S1P levels between the control and HIR groups, with a *P*-value of 0.002. Additionally, comparing the control group and the vehicle group showed statistical significant differences in the levels of MDA, raftlin, and S1P ($P=0.002$, $P=0.003$, and $P=0.002$, respectively). Furthermore, the RSV group exhibited higher MDA ($P=0.009$) and raftlin ($P=0.048$) and lower S1P ($P=0.005$) levels when compared to the control group. Statistically significant differences in MDA, raftlin, and S1P levels were observed between the HIR and Vehicle groups ($P=0.003$, $P=0.048$, and $P=0.002$, respectively), while all the three parameters showed

Table 1 — Comparison of Raftlin, MDA, and S1P Levels Across the Study Groups

	Control (n= 7)	HIR (n= 7)	Vehicle (n= 7)	RSV (n= 7)	*P*-Value
MDA nmol/protein	2.06 (1.8 – 2.6)	5.7 (4.6 – 6.3)	4.0 (3.6 – 4.7)	3.2 (2.3 – 3.5)	<0.001*
Raftlin pg/mL protein	402.0 (252.0 – 509.0)	995.0 (865.0 – 1143.0)	832.0 (495.0 – 1064.0)	502.0 (396.0 – 726.0)	<0.001*
S1P ng/mL protein	22.5 (19.7 – 25.0)	9.5 (8.6 – 11.3)	13.2 (12.0 – 14.8)	17.5 (14.5 – 20.7)	<0.001*

* Kruskal-Wallis test, $P<0.05$. MDA: malondialdehyde S1P: sphingosine-1-phosphate

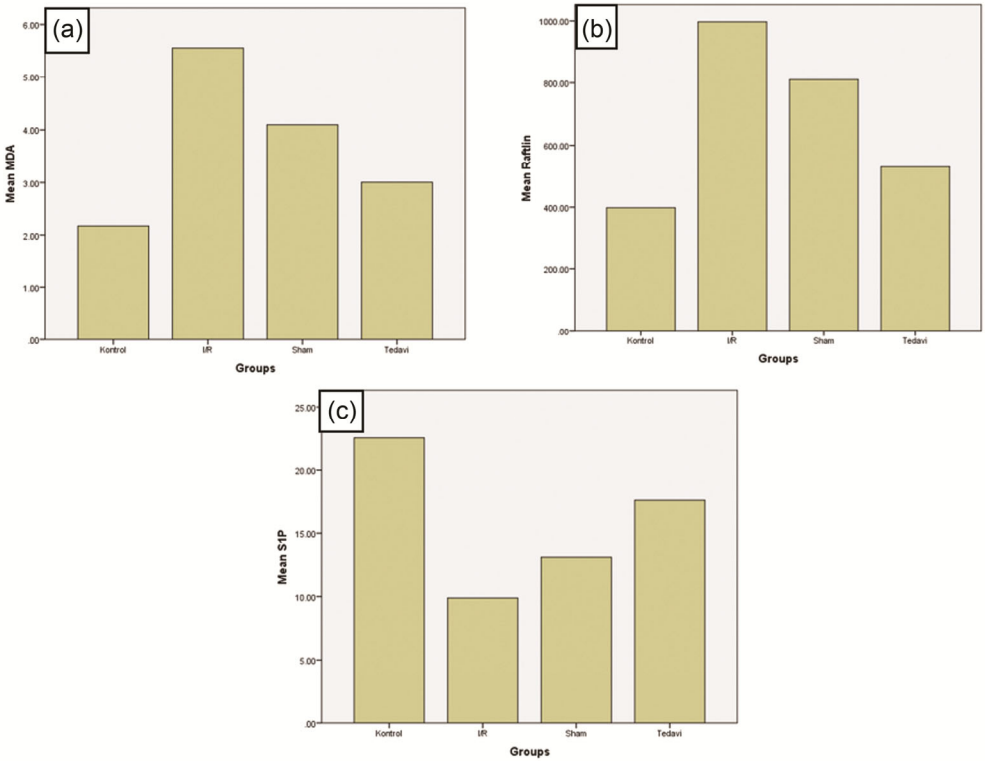

Fig. 1 — Levels of oxidative stress and inflammation parameters according to groups. A. MDA level B. Raftlin level C. S1P level. Malondialdehyde(MDA), sphingosine-1-phosphate(S1P).

Table 2 — Pairwise Comparisons between the Study Groups

Groups	MDA nmol/protein	Raftlin pg/ mL protein	S1P ng/mL protein
	P value	*P value*	*P value*
Control(n=7)	2.06 (1.8 – 2.6)	402.0 (252.0 – 509.0)	22.5 (19.7 – 25.0)
HIR(n=7)	5.7 (4.6 – 6.3)	995.0 (865.0 – 1143.0)	9.5 (8.6 – 11.3)
	*P=0.002**	*P=0.002**	*P=0.002**
Control(n=7)	2.06 (1.8 – 2.6)	402.0 (252.0 – 509.0)	22.5 (19.7 – 25.0)
Vehicle(n=7)	4.0 (3.6 – 4.7)	832.0 (495.0 – 1064.0)	13.2 (12.0 – 14.8)
	*P=0.002**	*P=0.003**	*P=0.002**
Control(n=7)	2.06 (1.8 – 2.6)	402.0 (252.0 – 509.0)	22.5 (19.7 – 25.0)
RSV(n=7)	3.2 (2.3 – 3.5)	502.0 (396.0 – 726.0)	17.5 (14.5 – 20.7)
	*P=0.009**	*P=0.048**	*P=0.005**
HIR(n=7)	5.7 (4.6 – 6.3)	995.0 (865.0 – 1143.0)	9.5 (8.6 – 11.3)
Vehicle(n=7)	4.0 (3.6 – 4.7)	832.0 (495.0 – 1064.0)	13.2 (12.0 – 14.8)
	*P=0.003**	*P=0.048**	*P=0.002**
HIR(n=7)	5.7 (4.6 – 6.3)	832.0 (495.0 – 1064.0)	13.2 (12.0 – 14.8)
RSV(n=7)	3.2 (2.3 – 3.5)	502.0 (396.0 – 726.0)	17.5 (14.5 – 20.7)
	*P=0.002**	*P=0.002**	*P=0.002**
Vehicle(n=7)	4.0 (3.6 – 4.7)	832.0 (495.0 – 1064.0)	13.2 (12.0 – 14.8)
RSV(n=7)	3.2 (2.3 – 3.5)	502.0 (396.0 – 726.0)	17.5 (14.5 – 20.7)
	*P=0.002**	*P=0.013**	*P=0.003**

*Mann-Whitney Test, $P<0.05$. MDA: malondialdehyde, S1P: sphingosine-1-phosphate, RSV:resveratrol, HIR: Hepatic ischemia–reperfusion

statistically significant differences between the HIR and RSV groups at the P=0.002 level. Finally, the differences between the Vehicle and RSV groups were shown to be statistically significant for MDA (P=0.002), raftlin (P=0.013), and S1P (P=0.003) (Table 2).

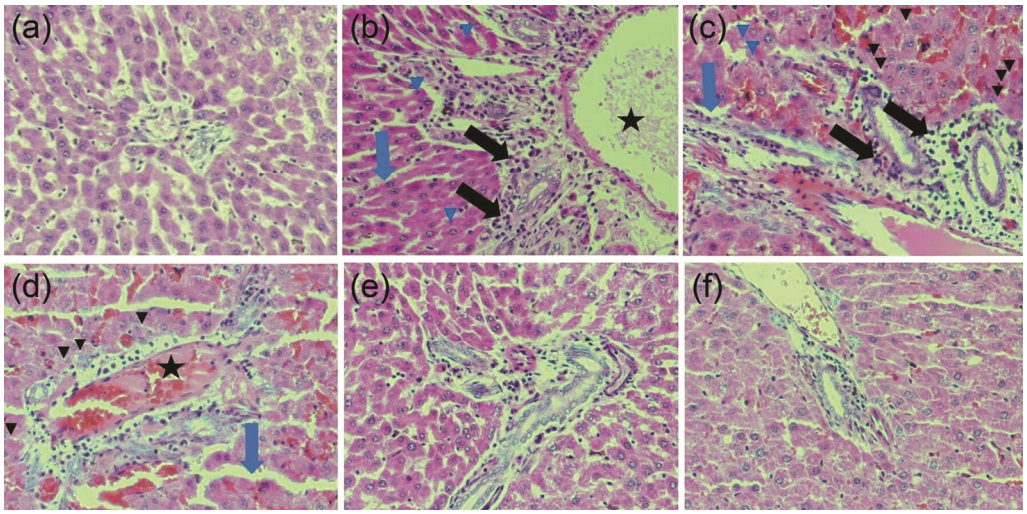

Fig. 2 — Micrographs of liver tissues. (a) Control, (b-c) HIR, (d) Vehicle, (e-f) RSV-treated*; Congestion in the central vein, Black arrow: Mononuclear cell infiltration, Blue arrow: Sinusoidal dilatation, Blue arrowhead: Vacuolarization, Black arrowhead: Hepatocytes with pyknotic nuclei RSV: resveratrol, HIR: Hepatic ischemia–reperfusion.

Histopathological Analyses

Based on histopathological examination, the liver parenchyma in the control group presented a normal appearance, with minimal findings of vascular congestion, sinusoidal dilatation, vacuolation, mononuclear cell infiltration, and necrosis. In contrast, the vehicle and I/R groups demonstrated a marked increase in the evaluated parameters. In particular, a severe increase in vascular congestion and sinusoidal dilatation, widespread vacuolation in hepatocytes, and the presence of necrotic hepatocytes were observed. On the other hand, the RSV treatment group showed a partially reversed histopathological damage, evidenced by a decrease in vascular congestion and inflammation and a large preservation of hepatocyte morphology (Fig 2).

Discussion

HIR damage, commonly observed in clinical conditions such as liver surgery and transplantation, plays a significant role in initiating serious pathophysiological processes such as oxidative stress, inflammation, apoptosis, and endothelial dysfunction[15,16]. I/R injury paradoxically occur during reperfusion after ischemia and further exacerbates the initial tissue damage. The limited understanding of the complex mechanisms underlying I/R injury hinders the development of effective therapeutic interventions[2]. The findings of this study suggest a possible involvement of resveratrol in modulating oxidative stress, inflammation, and sphingosine metabolism.

Biochemical Findings

HIR damage occurs in two distinct stages. The ischemia stage is characterized by ATP depletion and metabolic disorders leading to enhanced ROS production which consequently results in DNA and tissue damage. During the second stage, reperfusion, the excessive increase in proinflammatory mediators along with ROS further exacerbates HIR damage[17]. The basis of HIR damage involves increased oxidative stress and inflammatory response through the activation of Kupffer cells and the involvement of signaling pathways such as NF-κB and hypoxia-inducible factor 1-alpha (HIF-1α)[2]. In our study, MDA, which is considered a very good indicator of lipid peroxidation, was found to be statistically higher in the HIR and vehicle groups compared to the RSV and control groups (P<0.05) (Table 1 & 2, Fig 1). In a previous study in the literature, Bilge and Yildizhan reported that hepatic MDA levels of rat subjects exposed to 30 minutes of ischemia and 2 hours of reperfusion were significantly elevated compared to the control, sham, and taxifolin-treated rat groups[18]. Similarly, another study clearly demonstarted that MDA levels were higher in rats with HIR damage[19].

To the best of our knowledge, our study provides preliminary data on the raftlin protein, which has emerged as a potential biomarker for evaluating the inflammatory response associated with HIR damage. Group-wise comparisons revealed that raftlin levels, similar to MDA levels, were significantly elevated in the HIR and vehicle groups (P<0.05) (Table 1 & 2,

Fig 1). Studies employing comparable I/R models to evaluate the associated inflammatory response have investigated several established biomarkers. These include proteins such as Toll-like receptor-4 (TLR4) and liver fatty acid binding protein (L-FABP)[20], as well as complement system components C3, C5a, and C6[21]. Unlike these classical markers, raftlin is a newly recognized protein that is thought to play a significant role in immune cell signaling and inflammatory responses. Also, its potential as a biomarker is supported by the existing literature. A study by Guner *et al.* reported the high diagnostic values values of raftlin in patients with seborrheic dermatitis[22]. Moreover, in septic patients, raftlin blood levels were associated with sepsis severity and patient outcomes, suggesting that raftlin may serve as a novel marker for endothelial cell dysfunction[23]. In conclusion, the data obtained from the present study suggest that raftlin could be considered as a potential candidate biomarker for the assessment of HIR-associated inflammation.

S1P, one of the most important lysophospholipids that trigger a wide variety of cellular responses, plays both protective and harmful roles in the pathogenesis of inflammatory and metabolic diseases. Its effect varies depending on binding and signaling pathways[24,25]. The impact of S1P on endothelial cells is particularly important as it regulates vascular permeability. Existing literature suggests that S1P may limit inflammation by actively preserving endothelial barrier integrity[8,25]. Therefore, the potential effects of S1P in models causing acute liver damage, such as I/R, are noteworthy. In our study, S1P levels were found to be significantly lower in the HIR and treatment groups compared to the other study groups (Table 1 & 2, Fig 1).

In line with our findings, a previous study demonstrated that S1P levels were significantly reduced in the livers of mice subjected to I/R injury, while S1P levels tended to approach baseline values in the group treated with acid ceramidase. Similarly, another study showed that exogenous S1P administration reduced hepatic I/R damage in mice with a non-alcoholic fatty liver model[7]. Contrary to these findings, one study suggested that increased S1P and sphingosine kinase 1 expression increased I/R damage, revealing that S1P may also exhibit context-dependent harmful effects[26]. These changes in sphingolipid levels suggest that they may be related to differences in the activity of enzymes responsible for sphingolipid metabolism (e.g., SphK1, S1P lyase, ceramidase).

Histopathological Findings

Histopathological analyses conducted in the scope of the study revealed significant histopathological changes in the liver tissues of the groups subjected to HIR modeling (HIR and vehicle) (Fig 2). These changes included the presence of hepatocytes with dense pyknotic nuclei, indicating widespread necrosis, as well as mononuclear cell infiltration, reflecting morphological evidence of underlying inflammation. Furthermore, observations of central venous congestion demonstrated a serious impairment in hepatic microcirculation and the development of venous return obstruction. The presence of sinusoidal dilatation and vacuolization observed in some areas demonstrates damage to hepatocytes at both the vascular and cellular levels. These histopathological findings, particularly those observed in the HIR and vehicle groups, are a distinct manifestation of oxidative stress, inflammation, and cellular damage developing due to the ischemic process. Hepatic tissue damage and necrosis after I/R have also been reported by similar studies within the literature. In the study conducted by Durgun & Asir, rats were subjected to one hour of ischemia followed by six hours of reperfusion to create an HIR damage model. Histopathological analyses revealed marked alterations in liver tissue due to HIR damage, including histological changes such as hepatocyte degeneration, leukocyte infiltration, and sinusoidal dilatation[27]. Another study conducted on rats similarly reported that the liver morphologies of I/R-damaged rats showed significant variability in terms of hepatocyte vacuolation and degradation, sinusoidal dilatation, and neutrophil infiltration compared to other study groups[28].

One of the most significant findings in our study is that RSV treatment significantly reduced the histopathological damage caused by HIR. The reduction in vascular congestion and inflammation in the RSV group, the preservation of hepatocyte morphological integrity, and the limited extent of necrotic areas clearly support the potential the protective effect of RSV on the hepatic tissue. These observations are consistent with the established antioxidant and anti-inflammatory properties of RSV and, unlike previous studies in different animal models, demonstrate these effects in hepatic tissues

for the first time. In their study investigating the protective properties of RSV, Ozkan et al. presented data showing that RSV significantly reduced I/R damage in rat intestines[11]. In the I/R model, three doses of RSV were administered at 25, 50, and 100 mg/kg, respectively, and it was reported that it positively affected the histopathological results in all aspects[29]. These findings indicate that RSV can be considered as a potential treatment option against I/R injury in liver tissue.

Despite the significant findings, several limitations of this study should be acknowledged. First, although our results provide preliminary evidence in a rat model, the clinical translatability to human HIR injury requires further validation. Second, the study focused on a specific dose of resveratrol and fixed time intervals for the ischemia and reperfusion stages; thus, the effects of different dosage regimens and long-term outcomes remain to be explored. Additionally, while the alterations in raftlin and S1P levels offer novel insights, the detailed molecular pathways and potential receptor-level interactions through which resveratrol exerts its effects warrant further investigation in future studies.

Conclusion

Despite extensive research aimed at clarifying the complex mechanisms of HIR damage, its full pathophysiology remains to be completely understood. This study sought to contribute to this field by exploring the interplay model.

A notable finding of our research is the potential utility of raftlin as a novel indicator. Our data provide preliminary evidence suggesting that raftlin levels correlate with the inflammatory response in HIR, indicating it may serve as a promising candidate marker for evaluating tissue damage. Furthermore, the administration of RSV was observed to exert a protective influence, as evidenced by improved biochemical parameters and preserved histopathological structures. While these results underscore the potential therapeutic role of RSV in mitigating HIR damage, further clinical and molecular studies are warranted to fully validate these findings and elucidate the precise underlying mechanisms.

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Ethical approval:

The study was approved by the ethics committee of the Kahramanmaras Sutcu Imam University Experimental Animal Ethics Committee (Date: 27.02.2025, Decision number:01). All procedures performed in studies on animals were in compliance with ethical standards of the institution in which the studies were conducted and with the approved legal acts of the Russian Federation and international organizations.

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