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Network Pharmacology-based Investigation and Experimental Discovery of *Resveratrol's* Mechanism of Liver Ischemia Reperfusion-Induced Oxidative Stress Damage

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ABSTRACT

Background: This study aimed to investigate the hepatoprotective effect of RSV against oxidative stress damage and we induced an experimental liver Ischemia-reperfusion (I/R) model in rats.

Methods: Female albino rats were divided into three groups (n = 8). In contrast to the control group, 1 ml saline (0.09% NaCl) was administered intraperitoneally two days before the operation and after reperfusion in the sham group. 1 ml of 50 mg/kg Resveratrol was administered to the treatment group until two days before the operation. In addition, a single dose of 1 ml of Resveratrol was re-administered after reperfusion. The duration of liver ischemia/reperfusion was determined as 30 minutes in all groups. At the end of this experiment, antioxidant enzyme (CAT, SOD) activities and malondialdehyde (MDA) levels were measured as spectrophotometric in liver tissues homogenates.

Result: Our study observed tissue injuries in the ischemia/reperfusion and Sham groups ($p<0.001$). This study observed significant decreases in tissue MDA levels in the treatment group compared to the sham and control groups ($p<0.001$). In addition, antioxidant enzyme levels (SOD. CAT) were significantly increased in the treatment group compared to the control and Sham groups. Liver tissue samples were examined for hepatocyte damage and histopathological grade of the groups were shown. Our study observed tissue injuries in the ischemia/reperfusion and Sham groups ($p<0.001$). Liver edema, necrosis and PMNL infiltration were found to be decreased in the treatment group compared to the control group. The association of resveratrol with oxidative damage was also determined by network pharmacology analysis.

Key words: Liver CAT activity, Network analysis, PMNL infiltration, Resveratrol.

INTRODUCTION

In the last decade, there has been an increase in the rate of deaths due to liver diseases. The fact that the liver is in contact with other organs and fulfills many functions is proof of the vital importance of the liver. Ischemia-reperfusion injury (IRI) is a cellular injury that occurs after reoxygenation of the hypoxic organ. IRI in the liver was first observed in 1975 in experimental liver transplantation by Toledo-Pereyra *et al*. (1975).

Liver ischemia may occur in patients who have undergone surgery for trauma, cancer, biliary tract obstructions and strictures, apart from transplant surgery. It may also occur following a period of hemodynamic or cardiogenic shock without surgical intervention. The pathophysiology of liver IRI consists of the involvement of many mechanisms that lead to liver injury.

ROS are chemical derivatives that carry a single unpaired electron in their outer orbital. They are highly variable and easily react with inorganic and organic materials (Avnioglu *et al*., 2022). As long as the rate of ROS formation is in balance with the rate of the organism's defense systems consisting of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD), which neutralize or reduce them, the organism is not affected by free radicals. However, if the rate of radical formation exceeds the speed of the defense system, SOR starts to be harmful and emerges as oxidative stress in the organism (Senturk *et al*., 2008). Malondialdehyde (MDA) is the end product of lipid peroxidation and is formed from the peroxidation of fatty acids containing three or more double bonds. Formed MDA causes cross-linking of membrane compounds by affecting ion exchange from cell membranes and causes negative results such as change of ion permeability and enzyme activity.

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Because of this feature, MDA can react with the nitrogen bases of DNA and is therefore genotoxic and carcinogenic for mutagenic cell cultures (Demirhan *et al*., 2021).

Many hepatocyte protective agents are thought to be responsible for IRI; allopurinol, prostaglandin, hemoperfusion, aprotinin, methylprednisolone, deferoxamine and thrombocyte-activating factor antagonists, ubiquinone and platelet-activating factor, has been identified and their curative effects on IRI have been investigated in experimental IR models (Teoh and Farrell, 2003; Demirhan and Belge Kurutas, 2022).

Nowadays, the indiscriminate and frequent use of antibiotics has led to current health problems such as bacterial resistance to antibiotics. This situation led people to consume natural fruits and vegetables. Resveratrol (RSV) appears to be used as a popular dietary supplement in the treatment of various diseases. RSV (3,5,42 trihydroxystilbene) is a natural phytoalexin. Numerous experimental studies have shown the protective effects of RSV in the mechanism of various diseases such as cancer, viral infections, cardiovascular and inflammatory disease (Stvolinsky *et al*., 2000; Boldyrev *et al*., 1999; Zalesova and Kuleva, 1998; Russel and Dun, 2004; Okatani *et al*., 2003). RSV reduces oxidative stress by showing antioxidant, anti-apoptotic and anti-inflammatory effects.

Network pharmacology was first introduced in 2007 by Prof. Recommended by Hopkins (Hopkins, 2007). First, the idea arose that the pharmacological effects of drugs could be administered in network interaction rather than point-to-point. This newly developed approach changed how researchers studied the potential mechanisms of drugs and their pharmacological effects on certain diseases (Li and Zhang, 2013; Zhou *et al.,* 2020).

This study aimed to determine the hepatoprotective effect of RSV against oxidative stress damage by evaluating the biochemical and histopathological results of rats, for which we induced an experimental liver I/R model. However, we examined the relationship between RSV and liver ischemia for the first time with the Gene Network analysis.

MATERIALS AND METHODS

This research was carried out in the medicinal biochemistry laboratory of Kahramanmaras Sutcu Imam University between February and August 2022.

Animals

Wistar albino female rats were used in this study. The rats used in the experiment were provided with appropriate physical conditions in Kahramanmaras Sutcu Imam University Laboratory Animal Unit. The average weight of the rats given the optimum level of water and feed was measured as 210-300 g. The necessary permission was obtained from the ethics committee of Kahramanmaras Sutcu Imam University. Our study was completed safely and by the rules under the guidance of the National Institute of Health's Guide for the Care and Use of Laboratory Animals.

Experimental groups

The rats were divided into three groups and anesthesia was performed as intramuscular injection with ketamine (50 mg/kg).

I/R group (n = 8): Only ischemia-reperfusion group. Following intervention and surgery, 30 minutes of ischemia and 30 minutes of reperfusion were formed in the liver.

Sham group (n = 8): Median laparotomy was performed and the hepatic artery, portal vein and bile ducts were separated from the surrounding tissues. Intraperitoneal administration of 1 mL saline (0.9% NaCl) was begun two days before the procedure and 30 min of ischemia and 30 min of reperfusion were created. Following the reperfusion, 1 mL (single dose) of saline was given again.

Treatment group (n = 8): 1 ml RSV 50 mg/kg was administered intraperitoneally two days before the intervention and surgical procedure and 30 minutes of ischemia and 30 minutes of reperfusion were performed in the liver after the surgical procedure. Following the reperfusion, 1 ml (single dose) of RSV was administered again.

Operative details

Each experimental animal was fixed in the supine position on a warm and constant temperature dissection table and the rectal temperature was checked (Stangl *et al*., 2009). The surgical application area was cleaned with 70% ethyl alcohol. In all groups, the hepatic artery, portal vein and bile duct were visualized first. Sham group was closed without further action. Ischemia was performed on the experimental animals in the groups by stopping the blood flow for 30 minutes with the help of an anti-traumatic vascular clamp. To prevent the hypovolemic effects of the fluid lost during reperfusion, 0.5 ml of sterile saline was administered intraperitoneally into the abdominal cavity (Fridovich, 1974). Following this procedure, the muscle and skin incisions were sutured separately but continuously with 3/0 silk sutures and the incision area was closed. Each surgically treated experimental animal was kept alive for a 30-minute reperfusion period by being placed in chemically sterilized, single-individual, polycarbonate and transparent cages. Homogenate preparation and biochemical analysis were carried out medical biochemistry department of Kahramanmaras Sutcu Imam University. Histopathological analysis and evaluation were carried out at Kahramanmaras Sutcu Imam University, pathology department.

Preparation of homogenate

The tissues were homogenized with 1.15% KCl. The antioxidant enzyme activities (CAT, SOD) and MDA levels were measured after centrifugation at 14.000 rpm.

Biochemical analysis

SOD activity was measured according to the method of Fridovich (Fridovich, 1974). SOD activity was shown as U/mg protein. Cat activity was measured by the Beutler method (Beutler, 1984) and showed as U/mg protein.

This method expressed the decrease of hydrogen peroxide concentration at 230 nm. TBA test was used to measure MDA levels of tissues (Ohkawa *et al*., 1979).

Histopathological analysis

Each of the liver tissues taken for histological examinations during the dissection of the experimental animals was kept in a 10% formaldehyde solution in a tissue follow-up cassette for 24 hours. After the fixation process, using the routine histological follow-up method, 5 µm thick sections were taken from the tissue samples embedded in paraffin with the help of a microtome. Sections taken were stained using the hematoxylin-eosin staining method and the preparations were made permanent by closing with entellan. Histopathological examinations were performed at the level of light microscopy in H&E-stained liver sections.

Liver tissue samples were examined for hepatocyte damage. Changes in cell histology; liver edema, necrosis, hemorrhage and PMNL infiltration density were evaluated under light microscopy.

Statistical analysis

Statistical analysis made by SPSS (Statistical Package for Social Sciences) 24.0. Our results were given as mean±standard deviation. Kruskal-Wallis test and one-way analysis of variance were used to determine the differences among the groups. Statistically significant A p-value was considered less than 0.05.

Network-based analysis

Resveratrol predictive targets were obtained from a Swiss Target Prediction (http://www.swisstargetprediction.ch/). The online shiny go v0.75 database (http://bioinformatics.sdstate.edu/go75/) was used to identify oxidative damage targets. Then, the BIOLOGICAL PROCESS pathways of the common goals and the interrelationships of these pathways were analyzed.

RESULTS AND DISCUSSION

Biochemical results

The mean median values of SOD, CAT and MDA levels are shown in Table 1. Our study showed that there were significant differences in SOD, CAT and MDA levels among the I/R, sham and treatment groups (p: 0.001).

A decrease in the antioxidant activities (SOD and CAT) was seen in the I/R group compared to the other groups, however, the MDA level increased in this group (p: 0.001) (Fig 1, 2 and 3).

Histopathological results

When the liver sections of the sham group were examined, the vena central in the middle of the classical liver lobule, hepatocyte cords extending radially from the vena central to the periphery and sinusoids between these cords were noted. Sinusoids were observed in normal structure and width. In hepatocytes, the nucleus was round and mostly euchromatic and the cytoplasm was eosinophilic. In sinusoids, nuclei of endothelial cells were observed as flat and darkly stained. Kupffer cells, larger than endothelial cells, with oval nuclei and pale staining, were observed between the endothelial cells or attached to the surface facing the lumen. In the portal areas, the vena porta, arteria hepatica, bile duct and lymphatic vessel were normal.

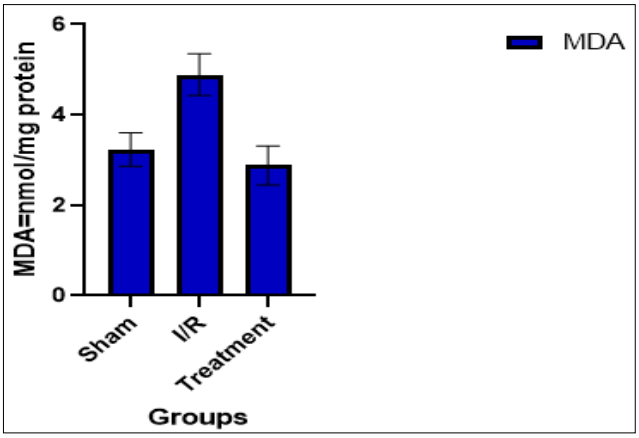


Fig 1: MDA levels of the groups.

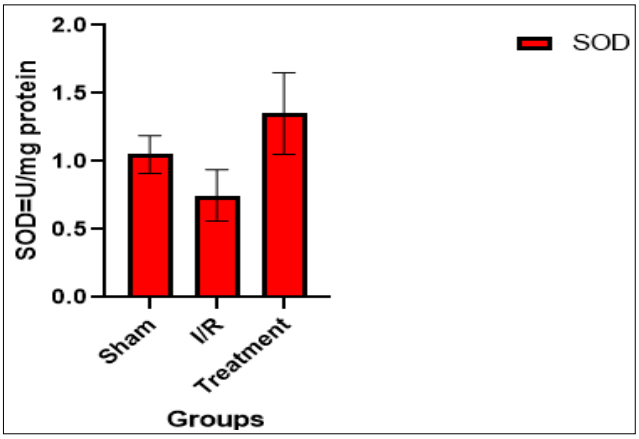


Fig 2: SOD levels of groups.

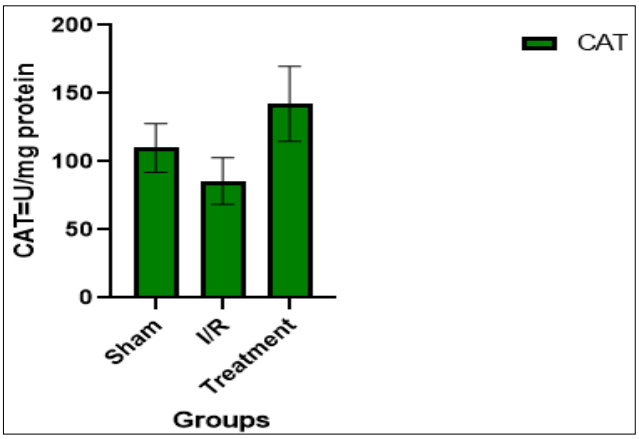


Fig 3: CAT levels of groups.

We have seen edema, necrosis, hemorrhage and multiple PMNL infiltration in the I/R group with histopathological examinations (Fig 4).

In the treatment group, histopathological evaluation was more regular compared to IR, with less dilatation of the sinusoids, less mononuclear cell infiltration and less degeneration of the hepatocytes. In addition, no focal necrosis was observed in the treatment group. It was observed that liver tissue was better preserved than the IR Group (Fig 4). Liver tissue samples were examined for hepatocyte damage and the histopathological grade of the groups were shown in Table 2.

Network pharmacology analysis

Among the Top 20 from the biological process pathway associated with oxidative damage reversible hydration of carbon dioxide, estrogen biosynthesis, biosynthesis of DHA-derived SPMs, biosynthesis of specialized pro-resolving mediators SPMs, metabolism of steroid hormones, metabolic disorders of biological oxidation enzymes, extranuclear estrogen signaling, cytochrome p450 arranged by substrate type, arachidonic acid metabolism, phase-I functionalization of compounds, biological oxidations, metabolism of lipids (Fig 5). The appropriate biological process pathway association for RSV is shown in Fig 6.

Hepatic ischemia-reperfusion injury can cause hepatic injury, which is seen in the setting of liver transplantation, trauma and liver surgery (Inglott *et al*., 2001; Vollmar *et al.,* 1996). Various mechanisms have been considered to explain the I/R injury of the liver. Increased ROS formation and secretion of inflammatory cytokines and proteolytic enzymes are one of the underlying mechanisms of liver I/R

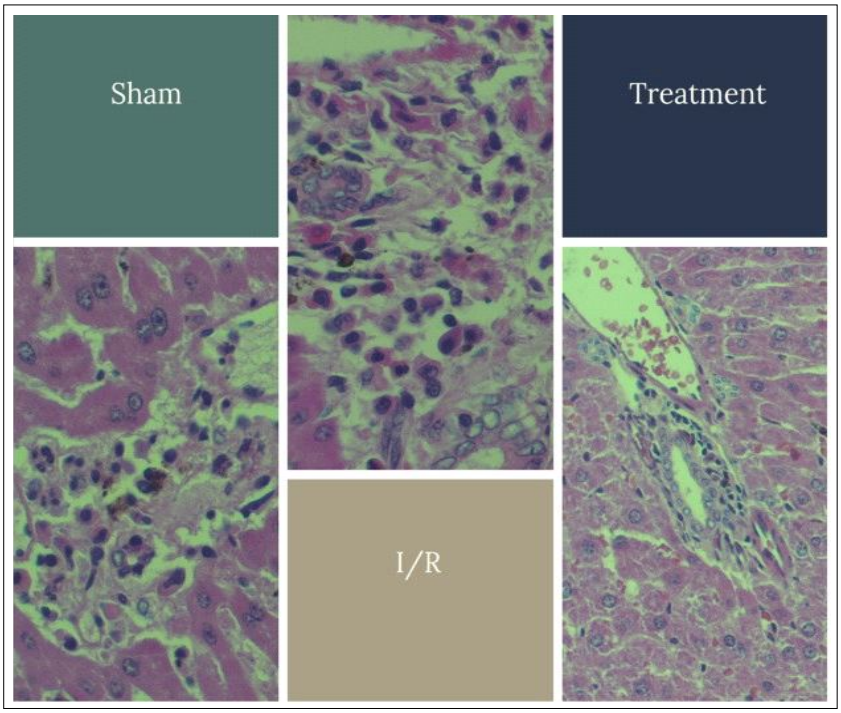


Fig 4: Histopathological images of the groups.

Table 1: Mean±median values of SOD, CAT and MDA levels.

Groups		MDA	SOD	CAT
Sham	Mean±Median	3.23±0.46	1.04±0.14	110.0±17.99
I/R	Mean±Median	4.89±0.47	0.75±0.19	85.63±17.05
Treatment	Mean±Median	2.88±0.43	2.31±0.43	142.25±27.51

Values are presented as mean±standard deviation.

Table 2: Histopathological grade of the groups.

	Liver **e**dema	Necrosis	Hemorrhage	PMNL infiltration
I/R	1	1	1	3
Sham	1	1	1	1
Treatment	0	0	1	0

injury (Martindale and Holbrook, 2002; Halliwell, 1999). An increased amount of ROS can initiate oxidative stress by causing lipid peroxidation (Krishnaswamy and Sushil, 2000). Elimination of oxidative stress, which is involved in the pathogenesis of many diseases, is very important to reduce tissue damage. Examples of SOD, CAT, Gpx and chemical compounds are α-tocopherol, ascorbic acid, carotenoid, coumarin and cinnamic acid derivatives (Kurutas, 2016). Superoxide dismutase (SOD), catalase (CAT) and glutathione are known endogenous antioxidants. However, these agents are not sufficient to reduce or eliminate oxidative stress. There are many studies in the literature investigating the protective effects of various exogenous antioxidants on liver I/R injury. Resveratrol (RSV), is containing the phytoalexin group which has antitumor, antiplatelet and estrogenic properties (Currin *et al*., 1991). RSV has antioxidant capacity due to the hydroxyl phenolic group it contains. RSV not only captures free radicals (hydroxyl radical, superoxide anion radical) but also increases the activity of antioxidant enzymes. The first studies on RSV were made on heart tissue. It is stated that it has cardioprotective effects on heart tissue by reducing or preventing I/R damage in the heart. *In vivo* and *in vitro* studies have shown that RSV is a very potent antioxidant

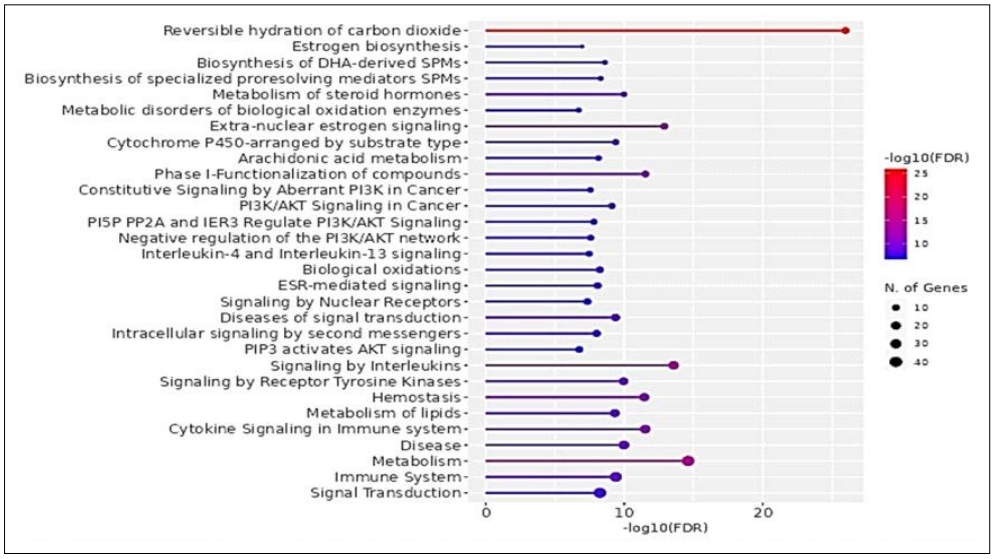


Fig 5: Biological process pathway suitable for resveratrol.

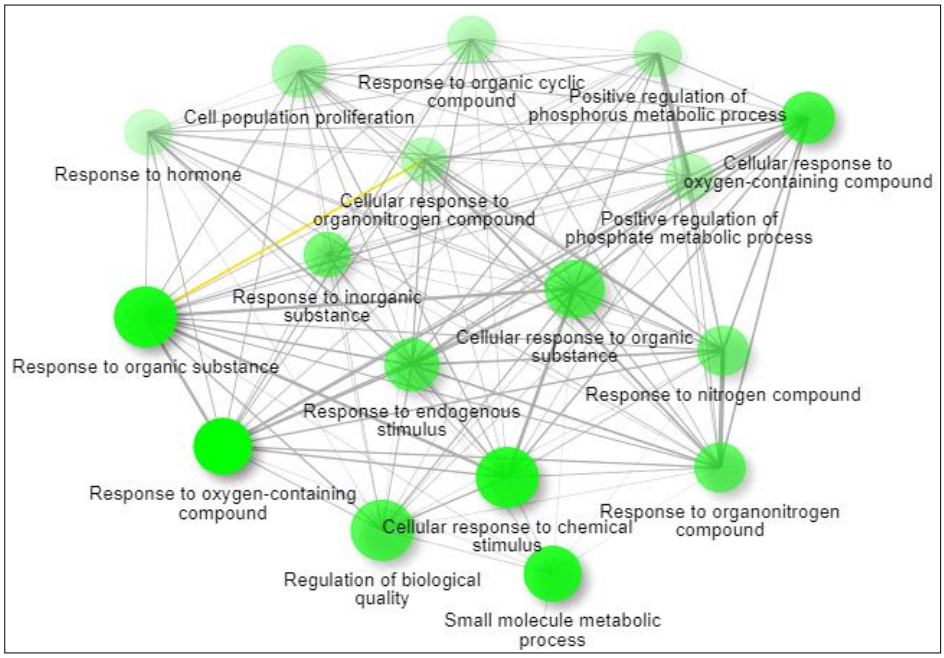


Fig 6: Appropriate biological process pathway association for resveratrol.

that can inhibit the formation of free radicals in the brain, spinal cord, kidney, liver and red cell membranes (Raghavan and Dikshit, 2004). It has been reported that RSV inhibits lipid peroxidation and inhibits apoptotic cell death caused by oxidative stress (Mahmood *et al*., 2018). The final production of lipid peroxidation includes aldehydes, hydrocarbon gases and MDA. MDA is a sensitive biomarker of interest in lipid peroxidation (Lancon *et al*., 2016).

With this study, we investigated the protective effects of RSV on I/R damage in the liver and biochemical and histopathological effects were examined. The results obtained from this study showed that the treatment of RSV may be effective in reducing both biochemical and histopathological damage due to liver I/R injury.

In our study, liver tissue MDA levels increased in the I/R group compared to the sham and treatment groups. We can say that the MDA levels of liver tissue decreased with resveratrol application, which means that RSV is effective in reducing oxidative stress. The increased MDA levels in the I/R group indicate that oxidant damage and the expected inflammation occur. SOD is the first enzyme involved in antioxidant defense against oxidative damage caused by superoxide (O_2-) radicals. The CAT enzyme converts H_2O_2 into harmless by-products. Therefore, they play an important role in the severity of cellular damage. This study showed that CAT and SOD enzyme activity levels increased in the treatment group compared to the I/R group. Increased SOD levels indicate that the effect of RSV converts O_2- radicals to less reactive H_2O_2. However, it can be said that the increased CAT enzyme activity in the RSV group prevents hydroxyl formation by catalyzing H_2O_2 into water. There are literature studies compatible with our research results (Zordoky *et al*., 2015; Faghihzadeh *et al.,* 2015; Elgebaly *et al*., 2017). In some studies, it was reported that SOD and CAT activity decreased in the treatment groups compared to the I/R group (Elgebaly *et al*., 2017). We can say that the differences between studies are probably due to differences such as experimental animal type, method and I/R model (ischemia and reperfusion time).

In our study, histopathologically, hepatocytes around the central vein showed normal structure in the liver section of the tissue samples belonging to the sham group, while degeneration, bleeding areas, dense necrosis, enlargement of the sinusoids, nuclear infiltration and cellular vacuolization were observed in the hepatocytes in the I/R group. These findings are encouraged by different studies (Baykara *et al*., 2009; Hassan-Khabbar *et al*., 2008).

Histopathological evaluations in the RSV treatment group (50 mg/kg) revealed nuclear infiltration, enlargement of sinusoids and decreased vacuolization and necrosis formation in hepatocytes.

We uncovered the biological mechanism of resveratrol by network pharmacology pathway analysis. It appears that RSV is the center of antioxidant protection in liver I/R injuries (Zhong *et al*., 2022).

CONCLUSION

Many mechanisms cause oxidative stress in living things. RSV, which is rich in polyphenols, is a good antioxidant. In our study, it was observed experimentally that RSV had a healing effect on liver I/R tissue damage. Both biochemical parameters and histopathological results showed that RSV protected the liver tissue by minimizing damage against oxidative stress.

Conflict of interest

All authors declare that they have no conflict of interest.

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