Resveratrol and liver: A systematic review

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Background: Recent studies demonstrated that resveratrol has many therapeutic effects on liver disorders. Resveratrol significantly increased survival after liver transplantation, decreased fat deposition, necrosis, and apoptosis which induced by ischemia in Wistar rats. It provided liver protection against chemical, cholestatic, and alcohol injury. Resveratrol can improve glucose metabolism and lipid profile and decrease liver fibrosis and steatosis. Furthermore, it was able to alter hepatic cell fatty acid composition. According to extension of liver disease around the world and necessity of finding new threat, this review critically examines the current preclinical *in vitro* and *in vivo* studies on the preventive and therapeutic effects of resveratrol in liver disorders. **Materials and Methods:** A search in PubMed, Google Scholar, and Scopus was undertaken to identify relevant literature using search terms, including "liver," "hepatic," and "Resveratrol." Both *in vivo* and *in vitro* studies were included. No time limiting considered for this search. **Results:** A total of 76 articles were eligible for this review. In these articles, resveratrol shows antioxidative properties in different models of hepatitis resulting in reducing of hepatic fibrosis. **Conclusion:** Resveratrol could reduce hepatic steatosis through modulating the insulin resistance and lipid profile in animals. These high quality preclinical studies propose the potential therapeutic implication of resveratrol in liver disorders especially those with hepatic steatosis. Resveratrol can play a pivotal role in prevention and treatment of liver disorders by reducing hepatic fibrosis.

Key words: Antioxidant, fibrosis, liver, liver dysfunction, liver disorders, liver transplantation, nonalcoholic fatty liver, resveratrol, steatosis

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INTRODUCTION

Resveratrol (3,4′,5-trihydroxy-trans-stilbene) was first isolated from the white hellebore by Takaoka in 1940 and then isolated from *Polygonum cuspidatum* (Japanese knot-weed) in 1963 by Nonomura.[1]

Resveratrol, a phytoalexin found in over 300 edible plants, including grapes, berries, and peanuts, is produced by plants as a defense mechanism against microbial injury, fungal infection or environmental stress.[2] It also found in red wine (0.1-15 mg/l), which proves, in part, the "French paradox" (the comparatively low incidence of cardiovascular disease in the French population despite regular consumption of a high-fat diet [HFD]), and may be responsible for many of the health benefits ascribed to red wine consumption.[3]

Subsequent studies have demonstrated that resveratrol can prevent or slow down the progression of a wide variety of illnesses, including malignancies, neurodegenerative diseases, cardiovascular ailments, ischemic injury, and viral infections.[4-7]

Resveratrol improved health and survival in obese mice,[8] and chronic liver diseases.[9] These findings suggested that resveratrol could therapeutically intervene with liver injury[10] and polyphenol-rich foods may serve as an adjuvant treatment in chronic liver diseases.[11]

The mechanisms underlying the beneficial effects of resveratrol are not totally elucidated, but have been related

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mainly to its antioxidant activity that has been demonstrated to protect tissues such as liver, kidney, and brain against a variety of damage caused by oxidative stress.[12]

According to extension of liver disease around the world and necessity of finding new threat, in this review, we studied the effects of resveratrol on liver both *in vivo* and in cell culture to help find novel therapeutic ways.

MATERIALS AND METHODS

We searched "PubMed," "Scopuse," and "Google Scholar" and used the following keywords: "Liver," "hepatic" and "resveratrol" [Figure 1]. Studies should be in English. Both *in vivo* and *in vitro* studies were included. No time limiting considered for this search. So, among 321 articles finally 76 articles were selected for this review. Study diagram is as follow:

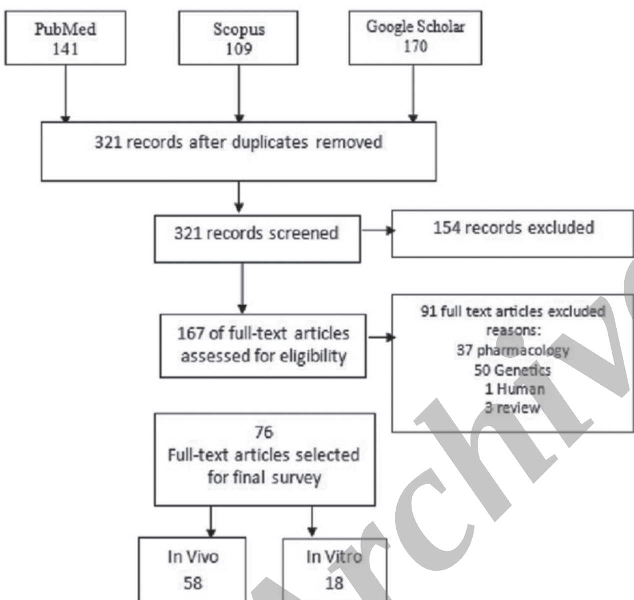

Figure 1: Study design

RESULTS

Several *in vivo* and *in vitro* studies provide evidence for the potential role of resveratrol as a hepatoprotective agent. The protective effects of resveratrol have been elucidated in animal and in both parenchymal (hepatocyte) as well as nonparenchymal liver cells such as stellate cells and Kupffer cells.

These studies are summarized in Table 1 (*in vitro* studies) and Table 2 (*in vivo* studies).

In vitro studies

Several *in vitro* studies [Table 1] have shown the hepatoprotective effects of resveratrol in different cell cultures. In human liver myofibroblasts trans-resveratrol markedly reduced proliferation of myofibroblasts in a dose-dependent manner and deactivated human liver myofibroblasts.[13] It also inhibited platelet-derived growth factor signaling via receptor inactivation, whereas it reduced epidermal growth factor-dependent DNA synthesis via inhibition of the phosphatidylinositol 3-kinase/Akt pathway, possibly through inactivity of phospho-inositide-dependent kinase-1.[14] Resveratrol inhibited HepG2 cellular triacylglycerol (TG) accumulation (which were incubated with high concentration of glucose and insulin) via activating AMP-activated protein kinase (AMPK) and downregulating sterol regulatory element binding protein 1c and fatty acid synthase gene expressions.[15] Nah *et al.*[16] showed that resveratrol effectively protects HepG2 cells from ethanol and hydrogen peroxide oxidative stress. Reduction in intracellular glutathione (GSH) depletion, cell proliferation, mitotic Cdk, malondialdehyde (MDA), reactive oxygen species (ROS) production, apoptosis, and cell death was also reported. Resveratrol amplifies the profibrogenic activation of human hepatic LX-2 stellate cells,[11] increases apoptosis and inhibits cell growth in hepatic stellate cells.[17] Resveratrol pretreatment effectively protected hepatocytes from oxidative stress,[18,19] increasing the activities of catalase (CAT), superoxide dismutase (SOD), GSH peroxidase (GPx), NADPH quinone oxidoreductase, and GSH-S-transferase.[18] Resveratrol also protected the cells against hydroquinone-induced toxicity through its antioxidant function and possibly a suppressive effect on the expression of cytochrome P450 2E1.[20] Relatively higher concentrations of resveratrol (≥1 mM) inhibited apoptosis of the mouse primary hepatocytes and increased cell viability in a dose-dependent manner, and in particular the survival rate of the hepatocytes was recovered from 28% to near 100% by 5 mM resveratrol.[20] In isolated hepatocytes from normal rats a resveratrol-induced short-term inhibition of fatty acids (specially formation of palmitic acid) and TG synthesis occurred.[21] Cerny *et al.*[22] have evaluated the effects of resveratrol as compared to silymarin pretreatments on tert-butylhydroperoxide (tBH) induced apoptotic/necrotic markers in hepatocytes. They found that resveratrol reduced hepatocyte necrotic and apoptotic effects caused by tBH and suggested that resveratrol has significant protective ability against tBH-induced oxidative damage. 10 μM resveratrol showed the similar effect of 500 μM silymarin. The authors concluded that resveratrol may play a chemopreventive role through antiapoptotic and antinecrotic effects via reducing nitric oxide synthase 2 (NOS-2) and hemoxygenase-1 in tBH-induced hepatocyte intoxication.[22] Effects of antioxidants, resveratrol, quercetin, and N-acetylcysteine on the functions of cultured rat hepatic stellate cells and Kupffer cells have been studied; resveratrol could have therapeutic potential against liver injury by regulating functions of hepatic stellate cells and Kupffer cells.[10] Resveratrol also had

Table 1: *In vitro* studies 1

Cell culture	Main result	Mechanisms of action	Concentration (μM)	Author/year
Human liver myofibroblasts	Trans-resveratrol markedly reduced proliferation of myofibroblasts in a dose-dependent manner. Trans-resveratrol can deactivate human liver myofibroblasts	↓expression of α-smooth muscle actin, ↓myofibroblast migration, ↓mRNA expression of type I collagen. It decreased the ↓secretion of matrix metalloproteinase 2	25/50/75/100 μmol	Godichaud *et al.*[13]
Human liver myofibroblasts	Resveratrol inhibits platelet-derived growth factor signaling	↓receptor activation of platelet-derived growth factor signaling		Godichaud *et al.*[14]
Cultured human HepG2 hepatocytes	Resveratrol could protect the liver from NAFLD[a]	↓TG, ↓SREBP-1c[b], ↓FAS[c], ↑phosphorylation of AMPK	50 μmol/L	Shang *et al.*[15]
Human liver adenocarcinoma cell line (HepG2)	Resveratrol effectively protects HepG2 and change liver cells from ethanol and hydrogen peroxide oxidative stress	↓intracellular GSH depletion, ↓cell proliferation, ↓mitotic Cdk, ↓MDA, ↓apoptosis and cell death, blocked ROS generation	50 μmol	Nah *et al.*[16]
HSCs	Resveratrol amplifies the profibrogenic activation of human hepatic LX-2 stellate cells	↑activation of human hepatic LX-2 stellate cells	15 μM	Bechmann *et al.*[11]
HSCs	Resveratrol inhibits cell growth	↓cell growth, ↑S-phase cell cycle arrest, ↑apoptosis	100 nM or 1 μM	Souza *et al.*[17]
Primary rat hepatocytes	Resveratrol could be a useful drug for the protection of liver cells from oxidative stress induced damage	↑activities of (CAT, SOD, GSH peroxidase, NADPH quinone oxidoreductase and GSH-S-transferase)	25, 50 and 75 μM	Rubiolo *et al.*[18]
Primary rat hepatocytes	Resveratrol protects primary rat hepatocytes from oxidative stress induced cell death	↓necrosis, ↓ROS	25, 50 or 75 μM	Rubiolo and Vega[19]
Mouse primary hepatocytes	Resveratrol protected the cells against hydroquinone-induced toxicity	↓apoptosis, ↑cell viability, ↓hydroquinone-induced expression of cytochrome P450 2E1 mRNA	0.5 or 1 or 5 mM	Wang *et al.*[20]
Rat hepatocyte	Resveratrol has hypolipidemic effect	↓total fatty acid, ↓formation of palmitic acid formation, ↓ACC[d] activity, ↓TGs	0-100 μM	Gnoni and Paglialonga[21]
Rat hepatocytes	Resveratrol reduced tBH[e]-induced hepatocyte toxic effects	↓ALT[f],↑NO[g],↓ NOS-2 and hemoxygenase-1 gene expression	10 μM	Cerný *et al.*[22]
Rat HSCs and Kupffer cells	Resveratrol may have therapeutic potential against liver injury by regulating functions of HSCs and Kupffer cells	↓NO, ↓TNF-α[h]	100 μmol/L	Kawada *et al.*[10]
Hepatoma G2 cells	Pretreatment with resveratrol blocked the apoptotic biochemical events	↓CTN[i]-induced cell apoptosis and oxidative stress, ↓ROS, ↓CTN-induced activation of caspases-3,-9, and PAK2[j]	5, 10, 20, 30, 40 μM	Chen and Chan[23]
Human hepatocyte-derived cancer cell line HepG2	Resveratrol inhibits the proliferation of HepG2 cells	↓cell proliferation, ↓ROS, ↑apoptosis, ↑iNOS and eNOS expression, ↑NOS activity, ↑NO production	10^{-7} M	Notas *et al.*[24]
HepG2 cells	Resveratrol inhibits proliferation of HepG2 cells	↓cyclin D1, ↓p38 MAP kinase, ↓Akt[k], ↓Pak1 expression, ↑ERK[l] activity	200 and 225 μM	Parekh *et al.*[25]
Human SK-HEP-1 hepatic cancer cells	Resveratrol causes hepatic cancer cell death	↓expression of antioxidant proteins, ↓ROS	225 μM	Choi *et al.*[26]
HepG2 HCC cells	PYB, trans-3,40-dihydroxy-20,30,5 trimethoxystilbene was more effective in inhibiting the growth of HepG2 HCC cells than resveratrol PYB could inhibit the invasion of HCC cells		50 μM	Wang *et al.*[3]
Liver of Wistar rats	Resveratrol plus ethanol counteract the ethanol-induced impairment of energy metabolism	Maintained ATP content, ↑mitochondrial ATP turnover, ↑sn-G3P[m]	20 _mol/L or (4.56 mg/L)	Gallis *et al.*[27]

[a]NAFLD = Nonalcoholic fatty liver disease; [b]SREBP-1c = Sterol regulatory element binding proteins 1c; [c]FAS = Fatty acid synthase; TG = Triacylglycerol; AMPK = AMP-activated protein kinase; GSH = Glutathione; [d]ACC = Acetyl-CoA carboxylase; [e]tBH = Tert-butylhydroperoxide; [f]ALT = Alanine aminotransferase; [g]NO = Nitric oxide; [h]TNF-α = Tumor necrosis factor alpha; [i]CTN = Citrinin; [j]PAK = Activated kinase; [k]Akt = Protein kinase B; [l]ERK = Extracellular signal-regulated kinases; [m]sn-G3P = sn-glycerol-3-phosphate; NOS-2 = Nitric oxide synthase 2; ROS = Reactive oxygen species; iNOS = Inducible nitric oxide synthase; eNOS = Endothelial nitric oxide synthase; HSCs = Hepatic stellate cells; PYB = Phoyunbene B; CAT = Catalase; SOD = Superoxide dismutase; HCC = Hepatocellular carcinoma

protective effects in carcinoma HepG2 cells. Pretreatment with resveratrol in these cells blocked the apoptotic biochemical events.[23] It also inhibited the proliferation of HepG2 cells.[24,25] Resveratrol causes hepatic cancer cell death by suppressing the expression of antioxidant proteins and reduction of ROS.[26] Wang *et al.* compared the effects of phoyunbene B (PYB) and resveratrol; they found that PYB, trans-3,40-dihydroxy-20,30,5 trimethoxystilbene) was more effective in inhibiting the growth of HepG2 hepatocellular carcinoma cells than resveratrol.[3] Resveratrol can also counteract the ethanol-induced impairment of energy metabolism by maintaining ATP content and increasing mitochondrial ATP turnover.[27]

In vivo studies [Table 2]

Liver transplantation

To study the effect of resveratrol on transplantation Wu *et al.* used Sprague–Dawley rats as donors and Wistar rats as recipients then 25, 50, and 100 mg/kg resveratrol was given once a day to the recipient mice. Increase in survival period and decrease in severity of rejection was seen in a larger dose of resveratrol as compared to the others.[28] Another study also reported an increase in survival period, decrease in the expression of protein kinase CΘ, ↓IκB kinase-β protein in lymphocytes.[29] Combination use of resveratrol (100 mg/Kg) and cyclosporine (20 mg/Kg) had better outcomes than cyclosporine alone.[30] This combination increased survival period and albumin and decreased serum total bile acid, alanine aminotransferase (ALT), serum interleukin-2 (IL-2) and interferon-γ (INF-γ) levels, activation of transcription factor nuclear factor-κB (NF-kB) peripheral blood T-lymphocytes and the severity of rejection. Resveratrol alone (100 mg/Kg) was able to increase survival period and albumin, and decrease serum total bile acid, ALT, IL-2, INF-γ, activation of transcription factor NF-κB and severity of rejection.[31]

Cancer and metastasis

Resveratrol could inhibit the growth of murine hepatoma 22, after the mice bearing H22 tumor were treated with 10 mg/kg or 15 mg/kg resveratrol for 10 days.[32] It also induced the S phase arrest of H22 cells and enhanced the anti-tumor effect of 5-FU on murine hepatoma 22.[32] Yu *et al.*[33] used murine transplanted hepatoma H22 model to evaluate the *in vivo* antitumor activity of resveratrol and reported that resveratrol exhibits anti-tumor activities on murine hepatoma H22. The underlying anti-tumor mechanism of resveratrol might involve the inhibition of the cell cycle progression by decreasing the expression of cyclin B1 and p34cdc2 protein.[33] Bishayee *et al.*[34] have examined the underlying mechanisms of resveratrol chemoprevention of hepatocarcinogenesis by investigating the effects of resveratrol on oxidative damage and inflammatory markers during diethylnitrosamine (DENA)-initiated rat liver carcinogenesis. In this study, resveratrol elevated the protein and mRNA expression of hepatic NF E2-related factor 2 (Nrf2). Resveratrol also reduced the hepatic iNOS protein expression and thiobarbituric acid reactive substances (TBARS) in these animals. It has been shown that resveratrol (50, 100 and 300 mg/kg) inhibits DENA-induced hepatocyte nodules in Sprague–Dawley rats in a dose-responsive manner.[35] Resveratrol exerts chemoprevention of hepatocarcinogenesis possibly through anti-inflammatory effects during DENA-evoked rat liver carcinogenesis by suppressing elevated levels of heat shock protein (HSP)70, COX-2 as well as NF-κB.[35] DENA-initiated hepatocarcinogenesis was suppressed by resveratrol administration for 20 weeks.[36] Resveratrol treatment reversed the DENA-induced alteration of the level and expression of hepatic tumor necrosis factor-alpha (TNF-α) and IL-1β and IL-6.[36] Luther *et al.*[2] also showed that long-term dietary administration of resveratrol dose-dependently suppressed hepatic tumor multiplicity.

Another study[37] investigated anti-inflammatory properties of resveratrol and reported that 1 mg/Kg resveratrol remarkably inhibited hepatic retention and metastatic growth of melanoma cells by 50% and 75%, respectively. The mechanism involved IL-18 blockade at three levels: First, resveratrol prevented IL-18 augmentation in the blood of melanoma cell-infiltrated livers. Second, resveratrol inhibited IL-18-dependent expression of VCAM-1 by tumor-activated hepatic sinusoidal endothelium, preventing melanoma cell adhesion to the microvasculature. Third, resveratrol inhibited adhesion and proliferation-stimulating effects of IL-18 on metastatic melanoma.

Hepatic glucose metabolism

Burgess *et al.*[38] studied the effect of resveratrol (100 mg/kg) on glucose metabolism in a Swine Model of Metabolic Syndrome induced by hypercholesterolemic diet. Increase in insulin receptor substrate 1, phosphorylated AKT, glucose transporter type 4 (Glut 4), peroxisome proliferating activation receptor-γ coactivator 1α, peroxisome proliferator-activated receptor-α, peroxisome proliferator-activated receptor-γ, phosphorylated AKT at threonine 308 expression and reduction in retinol binding protein 4 was seen according to resveratrol consumption.

Hepatic ischemia

Liver ischemia-reperfusion (I/R) injury occurs in many clinical conditions, including liver surgery and transplantation. Oxygen free radicals generated during I/R reduce endogenous antioxidant systems and contribute to hepatic injury. As resveratrol has antioxidant properties, different studies have conducted to examine the possible effect of resveratrol.

Table 2: *In vivo* studies 2

Subject	Author	Animal model	Drug dose	Duration	Main result
Transplantation	Wu *et al*.[28]	Sprague–Dawley rats as donors/Wistar rats as recipients			↑survival period, ↑longivity
	Wu *et al*.[29]	Sprague–Dawley rats as donors and Wistar rats as recipients			↑survival period ↓expression of PKCΘ[n], ↓IKKβ[o] protein in lymphocytes
	Wu *et al*.[30]	Sprague–Dawley rats as donors and Wistar rats as recipients			↑survival period ↑albumin, ↓serum total bile acid, ↓ALT[p],↓serum IL-2 and INF-γ levels, ↓activation of transcription factor NF-kB[q] n peripheral blood T lymphocytes, ↓ the severity of rejection
	Wu *et al*.[31]	Sprague–Dawley rats as donors and Wistar rats as recipients			↑survival period, ↑albumin, ↓serum total bile acid, ↓ALT, ↓IL-2[r],↓INF-γ, ↓activation of transcription factor NF-κB, ↓severity of rejection
Cancer and metastasis	Wu *et al*.[32]	Balb/c mice		10 days	Induce the S phase arrest of H22 cells and enhance the anti-tumor effect of 5-FU on murine hepatoma 22
	Yu *et al*.[33]	H22 tumour bearing mice		10 days	Anti-tumour activities, ↓expression of cyclinB1 and p34cdc2 protein. Blocking of S stage of tumour cells
	Bishayee *et al*.[34]	Sprague–Dawley rats		20 weeks	↓TBARS[s], ↓Nrf2, ↓hepatic iNOS protein expression
	Bishayee *et al*.[35]	Sprague–Dawley rats	50, 100 or 300 mg/kg	24 weeks	↓NF-κB, ↓HSP70[t], ↓COX-2[u]
	Mbimba *et al*.[36]	Sprague–Dawley rats	50, 100 and 300 mg/kg	20 weeks	↓hepatic TNF-α, ↓IL-1β, ↓IL-6
	Luther *et al*.[2]	Sprague–Dawley rats	50, 100 or 300 mg/kg	18 weeks	↓hepatic tumor multiplicity
	Salado *et al*.[37]	C57BL/6J mice	1 mg/kg	12 days	↓metastatic growth of melanoma, ↓IL-18, ↓expression of VCAM-1
Hepatic glucose metabolism	Burgess *et al*.[38]	Pigs/3 groups, control/ hypercholesterolemic diet (HCC)/hypercholesterolemic diet with supplemental resveratrol (HCRV)	100 mg/kg	11 weeks	↑insulin receptor substrate 1, ↑phosphorylated Akt, ↑Glut 4, ↑peroxisome proliferating activation receptor γ coactivator 1α, ↑peroxisome proliferator-activated receptor α, ↑peroxisome proliferator-activated receptor-γ, ↑phosphorylated Akt at threonine 308 expression, ↓retinol binding protein 4
Hepatic ischemia	Gedik *et al*.[39]	Sprague–Dawley rats	10 μmol/L		↑activity of aminotransferase. ↓MDA, ↓hepatic injury score, while ↑SOD, ↑CAT, ↑GSH, ↓histopathological changes in livers
	Hassan-Khabbar *et al*.[40]	Sprague–Dawley rats	0.02 or 20 mg/kg		↓ALT, ↓AST, ↑Cu/Zn-SOD and CAT Activities, ↑GSH, ↑GSH reductase, ↑Cu/Zn–SOD, and ↑ CAT activities
	Plin *et al*.[41]	Wistar rats			↓lipid peroxidation, protects mitochondrial functions, ↑respiratory chain activity, ↓activation of the cellular markers of necrosis and apoptosis
Hepatic Chemical injury	Rivera *et al*.[42]	Wistar rats	10 mg/kg		↓GSH, ↓GSH/GSSG ratio were decreased by CCl_4; both effects were completely prevented by any of the compounds tested ↓lipid peroxidation, ↓activity of γ-glutamyl transpeptidase, ↓ALT
	Fan *et al*.[43]	Swiss albino mice	30 mg/kg	Single dose	↓AST, ↓ALT, ↓SALP, LDH, ↓γ-GT and ↓CK, ↓total bilirubin, ↓urea and ↓uric acid, ↓hepatic peroxidative stress, ↑GSH, ↓GSSG
	Lodovici *et al*.[44]	Fisher 344 rats	50 mg/kg	14 days	↓SOD, ↓XO[v], ↑GSH/GSSG
	Tunali-Akbay *et al*.[45]	Wistar albino rats	20 mg/kg	5 days	↓hepatic MDA, ↓ALT, ↓AST, ↓TNF-α, ↓LDH, ↑liver GSH
	Roy *et al*.[46]	Wistar rats	100 or 200 mg/kg	8 weeks	↓TNF-α, ↓IL-6, ↓liver MDA, ↓hepatocyte nodules, ↓apoptosis
	Vitaglione *et al*.[47]	Sprague–Dawley rats	3 mg/kg	14 days	↓lipid peroxidation (↓MDA)

(Contined)

Table 2: (Continued)

Subject	Author	Animal model	Drug dose	Duration	Main result
Hepatic toxicity	El-Agamy[48]	Fischer rats	10 mg/kg BW	90 days	No effect on aflatoxin B1-induced liver injury
	Hamadi *et al.*[49]	Sprague–Dawley rats	10 mg/kg	15 days	↓blood glucose, ↓mortality, ↓AST, ↓ALT, ↓total bilirubin, ↓TC[w], ↓TG, ↓LDL[x], ↓TC/HDL[y], ↑SOD, ↑CAT, ↑GST[z], ↑QR*
Hepatic cholestatic injury	Chan *et al.*[50]	C57BL/6 mice	4 mg/kg	3 days or 7 days	↓ALT, ↓AST, ↓TNF-a, ↓IL-6 mRNA, ↓number of Kupffer cells (CD681) in the injured liver, ↓hepatic fibrosis, ↓reduced collagen Ia1, ↓TIMP-1 mRNA ↓inflammation, ↓activation of Kupffer cells, ↓fibrosis, ↑hepatocyte regeneration
Irradiation-induced hepatic injury	Velioglu-Ogünç *et al.*[51]	Sprague–Dawley rats	10 mg/kg	20 days	↑GSH level, ↓MDA, ↓myeloperoxidase activity, ↓collagen content, ↓plasma LDH, ↓pro-inflammatory cytokine levels, ↓leukocyte apoptosis
Hepatic injury after trauma-hemorrhage	Yu *et al.*[52]	Sprague–Dawley rats	30 mg/kg	Single dose	↓myeloperoxidase activity, ↓ICAM-1, ↓IL-6, ↓ALT, ↓AST
Heoatic alcohol injury	Bujanda *et al.*[53]	Balb/c mice/four groups (control, resveratrol-treated control, alcohol and resveratrol-treated alcohol)	10 mg/ml in drinking water	6 weeks	↓ALT, ↓AST, ↓IL-1, ↓severity of liver lesions, ↓mortality
	Kasdallah-Grissa *et al.*[54]	Wistar rats	5 g/kg food	6 weeks	↓hepatic lipid peroxidation, ↑SOD**, ↑GPx and ↑CAT activities in the liver
	Jinghui and Yingbao[55]		25, 50 or 100 mg/kg	7 days	↓TNF-α, ↓IL-6, ↓ICAM-1, ↓liver NFκB p65, ↓phosphorylating IκB-α
Hepatic oxidative damage	Schirmer *et al.*[56]	Zebrafish	5 or 50 mg/l	30 or 60 min	↓expression levels of the SIRT3, SIRT4, and NAMPT genes. ↑NADH levels, ↓NAD⁺/H
	Schmatz *et al.*[12]	Streptozotocin-induced diabetic rats	10 or 20 mg/kg	30 days	↓TBARS, ↑activities of CAT, SOD and d-ALA-D and the levels of NPSH and Vitamin C ↓ALT, ↓AST and ↓g-glutamiltransferase (g-GT) activities ,↓urea, ↓creatinine, ↓cholesterol, ↓triglycerides, ↓lipid peroxidation
	Chang *et al.*[57]	Long–Evans rats	0.1 or 1 mg/kg	7 days	↓superoxide anion, PCL and Mn-SOD protein expression in the hepatic tissues, ↓activated form of NF-κB, ↓hepatic IL-1β
	Sebai *et al.*[58]	Wistar rats	20mg/kg	7 days	↓LPS-induced lipoperoxidation, ↑SOD, ↑CAT, ↑glutathione peroxidase (GPx) activity, ↓NO, ↓endotoxemia-induced hepatic tissue injury, ↓liver iron
	Rocha *et al.*[59]	Wistar rats	1 mg/kg	30 days	↓glucose level, ↑SOD, ↓ox-LDL, ↓hepatic oxidative stress. In standard-fed-rats reduced ↓GSH-antioxidant defense system and ↑hepatic lipid hydroperoxide
	Bagul *et al.*[60]	Sprague–Dawley rats	10 mg/kg	8 weeks	↓blood glucose, ↓triglyceride, ↓uric acid, ↓NO, ↓TBARS
	Palsamy *et al.*[61]	Wistar rats	30 days	5 mg/kg b.w.	↓TNF-α, ↓IL-1β, ↓IL-6, ↓NF-κB, ↓liver NO, ↓lipid peroxides, ↓hydroperoxides, ↓protein carbonyls, ↑activity of (SOD, CAT, GPx, GST and GR)
	Upadhyay *et al.*[62]	Swiss albino mice	10 mg/kg	1–4 weeks	↓ALT, ↓AST, ↓lipid peroxidation
	Farghali *et al.*[63]	Wistar rats	2.3 mg/kg i.p (10 lmol/kg)	Single dose	↓ALT, ↓AST, ↓α-GST, ↑CAT, ↓TBARS, ↓conjugated dienes
	Kirimlioglu *et al.*[64]	Wistar albino rats	30 mg/kg	7 days	↓PH-induced lipid peroxidation, ↓hepatic GSH, ↓NO
	Sengottuvelan and Nalini[65]	Wistar rats	8 mg/kg	30 weeks	↓activity of SOD, CAT, Gpx, GST and GR, ↓GSH, Vitamin C, Vitamin E levels

(Contined)

Table 2: (Continued)

Subject	Author	Animal model	Drug dose	Duration	Main result
Hepatic heat stress	Sahin *et al.*[66]	Japanese quails	200 or 400 mg/kg of diet	12 weeks	↓MDA, ↑activities of SOD, CAT and GSH-Px, ↑feed intake, egg production, ↑Nrf2 expression, ↓Hsp70, Hsp90 and NF-κB expression
Hepatic Steatosis	Xin *et al.*[67]	Wistar rats	50,100 mg/kg	13 weeks	Unexpectedly, ↑hepatic FAS gene expressions, up regulation of hepatic LDLr and SR-BI gene expressions
	Kopeć *et al.*[68]	Wistar rats	0.04% or 0.06%	4 months	↓liver weight, ↓liver fat concentration, ↓steatosis, ↓TBARS, ↓MDA
	Poulsen *et al.*[69]	Wistar rats	100 mg resveratrol	8 weeks	↑hepatic uncoupling protein 2 expression
	Alberdi *et al.*[70]	Sprague–Dawley rats	30 mg/kg	6 weeks	↓liver fat accumulation, ↑CPT-Iα and ACO, ↓ACC activities. ↑activaty of AMPK and PGC-1α
	Cho *et al.*[71]	C57BL/6J mice	0·005 or 0·02% (w/w)	10 weeks	↓visceral fat, ↓plasma NEFA, ↓liver TAG and cholesterol, ↓lipid droplet number and size, ↓body weight gain, ↓plasma TAG, ↓total cholesterol
	Bujanda *et al.*[72]	Wistar CRL: Wi (Han) male rats	10 mg/d	4 weeks	↓fat deposition, ↑TNFα, ↑MDA, ↑SOD, ↑GSH peroxidase, ↑CAT, ↓NOS, ↓glucose
	Ajmo *et al.*[73]	C57BL/6J mice	200 or 400mg/kg	4 weeks	↑SIRT1 expression levels, ↑AMPK activity in livers, ↓SREBP-1, ↑PGC-1α, ↑adiponectin, ↑mRNA expression of hepatic adiponectin receptors (AdipoR1/R2)
	Shang *et al.*[15]	Wistar rats	100 mg/kg	10 weeks	↓hepatic TG, ↓SREBP-1c, ↓FAS, ↑phosphorylation of AMPK
	Shiozaki *et al.*[74]	mouse P10 (SAMP10)	0.04% resveratrol	20 weeks	↓lipid droplets, ↑mitochondria number, ↑SOD2
	Zhu *et al.*[75]	Sprague–Dawley rats	30 and 70 mg/kg	4 weeks	↓serum lipid, ↓hepatic TC, ↓TG ↑bile acids, ↓hepatic TBARS, ↑SOD, ↑glutathione peroxidase (GSH-Px), ↑CAT
	Chen *et al.*[76]	C57BL/6 J mice	200 mg/kg	8 weeks	↓body weight, ↓liver weight, ↓hepatic cholesterol accumulation, ↓total cholesterols, ↓LDL-C, ↑HDL-C, ↓LDL-C/HDL-C
	Miura *et al.*[77]	Donryu rats	10 or 50 ppm	20 days	↓TG, ↓VLDL, ↓LDL, ↓TBARS, ↓metastasis
Liver Fibrosis	Di Pascoli *et al.*[78]	Wistar rats	10 and 20 mg/kg	2 weeks	↓portal pressure, improved vasodilatory response to acetylcholine, ↓TXA2 production, ↑eNO, ↓liver fibrosis, ↓collagen-1, TGF-β, ↓NF-κB mRNA expression, ↓desmin and α-SMA protein expression
	Hong *et al.*[79]	Sprague–Dawley rats	10 mg/kg	7 days	↓infiltration of inflammatory cells and fibrosis of liver tissue. ↓MDA, ↑glutathione peroxidase, ↑SOD. ↓mRNA expression of inflammatory mediators (iNO, tumor necrosis factor-alpha and interleukin-1beta) ↓mRNA expression of fibrosis-related genes such as TGF-β 1, collagen type I, and alpha-smooth muscle actin, ↓hydroxyproline
	Lee *et al.*[80]	Sprague–Dawley rats	20 mg/kg	4 weeks	↓alanine transaminase, ↓aspartate transaminase, ↓alkaline phosphatase, ↓bilirubin, ↑albumin, ↑hepatic glutathione, ↓hepatic MDA, ↓hydroxyproline, ↓type I collagen mRNA expression, ↓HSC activation, ↓transforming growth factor-β1 mRNA expression
	Lv *et al.*[81]	Wistar rats	25,50 or 100 mg/kg	6 weeks	↓ALT, ↓liver hydroxyproline, ↓MDA, ↓liver fibrogensis

[n]PKCΘ = Protein kinase CΘ; [o]IKKβ = IκB kinase-β; [p]ALT = Alanine aminotransferase; [q]NF-κB = nuclear factor-κB; [r]IL-2 = Interleukin-2; [s]TBARS = Thiobarbituric acid reactive substances; [t]HSP70 = Heat shock protein 70; [u]COX-2 = Cyclooxygenase-2; [v]XO = Xanthine oxidase; [w]TC = Total cholesterol; [x]LDL = Low density lipoprotein; [y]HDL = High density lipoprotein; [z]GST = Super oxide dismutase; *QR = Quinone reductase; **SOD = Superoxide dismutase. Nrf2 = NF E2–related factor 2; iNOS = Inducible nitric oxide synthase; TNF-α = Tumor necrosis factor alpha; VCAM-1 = Vascular cell adhesion molecule 1; Akt = Protein kinase B; Glut 4 = Glucose transporter type 4; MDA = Malondialdehyde; IL-1 = Interleukin-1; IL-1β = Interleukin-1 beta; SALP = Serum alkaline phosphatase; LDH = Lactate dehydrogenase; INF-γ = Interferon-γ; AST = Aspartate aminotransferase; GSH = Glutathione; GSSG = Glutathione disulfide; CCl_4 = Carbon tetrachloride; CK = Creatine kinase; TG = Triacylglycerol; CAT = Catalase; TIMP-1 = Tissue inhibitor of metalloproteinases-1; ICAM-1 = Intercellular adhesion molecule 1; IκB-α = Inhibitor of kappa B; SIRTs = Sirtuins; d-ALA-D = Aminolevulinic acid dehydratase; NPSH = Nonprotein thiols; NO = Nitric oxide; ox-LDL = Oxidized low-density lipoprotein; GR = Glutathione reductase; PH = Partial hepatectomy; FAS = Fatty acid synthase; LDLr = Low density lipoprotein receptor; SR-BI = Scavenger receptor class B type I; CPT-Iα = Carnitine palmitoyl transferase-Iα; ACO = Acyl-coenzyme A oxidase; ACC = Acetyl-CoA carboxylase; AMPK = AMP-activated protein kinase; PGC-1α = Peroxisome proliferator-activated receptor-γ coactivator α; SREBP-1 = Sterol regulatory element binding protein 1; SREBP-1c = Sterol regulatory element binding proteins 1c; LDL-C = Low-density lipoprotein cholesterol; HDL-C = High-density lipoprotein cholesterol; VLDL = Very-low-density lipoprotein; eNOS = Endothelial nitric oxide synthase; TGF-β = Transforming growth factor beta; HSCs = Hepatic stellate cells; HCC = Hepatocellular carcinoma γ-GT

Gedik *et al.*[39] investigated the effects of resveratrol (10 μmol/L) on the liver I/R injury in rats. Rats underwent liver ischemia for 45 min followed by reperfusion for 45 min. They reported that the activity of aminotransferase increased by resveratrol supplementation, while significant decrease in MDA, hepatic injury score and histopathological changes in livers and elevation in SOD, CAT, GSH resveratrol were occured.

Another study by Hassan-Khabbar *et al.*[40] showed decrease in aminotransferase levels by about 40% and improvement of sinusoidal dilatation. In this study, trans-resveratrol preserved antioxidant defense by preventing total and reduced GSH depletion caused by I/R. At 0.2 mg/kg, trans-resveratrol significantly increased GSH reductase, Cu/Zn–SOD, and CAT activities. However, at a high dose (20 mg/kg), trans-resveratrol became prooxidant with an aggravation of liver injury evaluated by aminotransferase release and histological analysis and associated with a depletion of total and reduced GSH levels and a decrease of antioxidant enzyme activities.

Plin *et al.*[41] investigated the effect of the natural phytoalexin resveratrol on the prevention of liver injuries induced by 40-h cold preservation followed by a warm reperfusion. They concluded that resveratrol inhibits lipid peroxidation and protects mitochondrial functions. It improves respiratory chain activity and prevents opening of the permeability transition pore, allowing better recovery of ATP energetic charge. Resveratrol also limits the activation of the cellular markers of necrosis and apoptosis.

Postischemic treatment with resveratrol (0.02 and 0.2 mg/kg) resulted in a significant decrease in aminotransferase, IL-1b and IL-6 plasma levels by about 40%, 60%, and 40%, respectively, compared to the vehicle I/R group.[82]

Hepatic chemical injury

Rivera *et al.*[42] examined the effect of resveratrol and trimethylated resveratrol on hepatotoxicity induced by carbon tetrachloride (CCl_4). The GSH/GSSG (oxidized GSH) ratio decreased in the groups receiving CCl_4 and resveratrol associated with an increase in GSSG. In blood GSH and the GSH/GSSG ratio were decreased by CCl_4; both effects were completely prevented by any of the compounds tested. Lipid peroxidation and the activity of γ-glutamyl transpeptidase were increased significantly after CCl_4. Resveratrol partially prevented these increases and surprisingly, trimethylated resveratrol completely prevented the increase of these markers. Both compounds partially but significantly prevented the increase in the activity of alanine aminotransferase.

In another study, resveratrol was able to mitigate hepatic damage induced by acute intoxication of CCl_4 and showed pronounced curative effect against lipid peroxidation and deviated serum enzymatic variables as well as maintained GSH status toward control.[43]

In a model of chemically induced acute hepatic injury, resveratrol at dose of 50 mg/kg/day administered for 14 days long could ameliorate hepatic injury by its antioxidant and scavenging properties, through a reduction of xanthine oxidase activity, a partial restoration of GSH/GSSG ratio in addition to its capacity to inhibit apoptosis.[44]

To investigate the possible protective effect of resveratrol on some liver and blood parameters in methotrexate (MTX) induced toxicity in rats, Tunali-Akbay *et al.*[45] administered resveratrol (10 mg/kg, orally) for 5 days after a single dose of MTX. The results showed that MTX administration increased the hepatic enzymes, TNF-α, MDA, myeloperoxidase and tissue factor activities and collagen contents and decreased GSH, while all of these alterations were reversed by resveratrol.

Roy *et al.*[46] also examined the chemopreventive potential of resveratrol in rat hepatic injury model by CCl_4. Resveratrol (100 mg/kg, or 200 mg/kg body weight) was given orally for 8 weeks. They reported that resveratrol decreased the immunopositivity of TNF-α and IL-6 and restored the altered architectural structure of challenged hepatic tissue. Resveratrol also protected hepatic cells by suppressing oxidative stress and apoptosis.

Vitaglione *et al.*[47] investigated the effect of resveratrol on an animal model of CCl_4-induced liver lipid peroxidation. Grape-stalk extract determining a daily resveratrol dosage of 3 mg/kg was given to the rats for 14 days. Resveratrol could reduce liver concentration of MDA after 24 h and 1-week by 38% and a 63%, respectively.

Hepatic toxicity

Aflatoxin B1 is a potent hepatotoxic and hepatocarcinogenic mycotoxin. Lipid peroxidation and oxidative DNA damage are the principal manifestations of afatoxin B1-induced toxicity that could be counteracted by antioxidants. El-Agamy[48] compared the effect of curcumin (polyphenolic antioxidant purifed from turmeric) and resveratrol for possible protection against liver injury induced by afatoxin B1 in rats. Results showed that curcumin showed a significant hepatoprotective activity by lowering the levels of serum marker enzymes, lipid peroxidation and elevating the levels of GSH, SOD, CAT, and GSH-Px. However, resveratrol failed to protect from the afatoxin B1-induced liver injury. Resveratrol (10 mg/kg) for 15 days in streptozotocin (STZ)-induced diabetic rats has shown hepatoprotective effects against diabetes-induced liver damage via reduction of serum glucose level and oxidative damage and improving serum lipid profile.[49]

Hepatic cholestatic injury

Liver injuries can trigger a cascade of inflammatory responses and as a result, initiate the process of hepatic regeneration and fibrogenesis. To study the potential protective effects and mechanism of resveratrol on cholestatic liver injury, resveratrol was given (4 mg/kg/day) for either 3 days or 7 days after bile duct ligation (BDL) injury. Resveratrol significantly reduced serum ALT, aspartate aminotransferase (AST) but not bilirubin on day 3. At this early stage of injury, resveratrol significantly reduced TNF-α and IL-6 mRNA and decreased the number of Kupffer cells (CD681) recruited in the injured liver. It also decreased hepatic fibrosis. Totally resveratrol attenuated inflammation and reduced Kupffer cells activation leading to decrease in fibrosis and promotion of hepatocyte regeneration, which increased the survival of BDL mice.[50]

Irradiation-induced hepatic injury

Velioğlu-Öğünç *et al.*[51] studied the effects of resveratrol on ionizing radiation-induced oxidative injury. After 10 days pretreatment with resveratrol (10 mg/kg), rats were exposed to whole-body IR (800 cGy) and the resveratrol treatment was continued for 10 more days after the irradiation. Resveratrol caused a significant increase in GSH level, while MDA levels, myeloperoxidase activity and collagen content decreased in hepatic tissues. Similarly, plasma lactate dehydrogenase and pro-inflammatory cytokine levels, 8-hydroxy-2′-deoxyguanosine and leukocyte apoptosis decreased, while antioxidant-capacity increased in the irradiated rats with resvratrol as compared with the control group. Resveratrol treatment reversed histopathological alterations induced by irradiation.[51]

Hepatic injury after trauma-hemorrhage

Resveratrol administration after trauma-hemorrhage attenuated hepatic injury, likely through reduction of proinflammatory mediators. Resveratrol-mediated hepatic preservation seemed to progress via an estrogen receptor (ER) related pathway.[52]

ALCOHOLIC LIVER INJURY

Bujanda *et al.*[53] investigated the effect of resveratrol on alcohol-induced mortality and liver lesions in mice. They compared the effect of consuming alcohol, alcohol and resveratrol, and resveratrol alone. Transaminase concentration was significantly higher in the alcohol group than in the other groups. IL-1 levels were significantly reduced in the alcohol plus resveratrol group compared with the alcohol group. Histologically, the liver lesions were more severe in the alcohol group, though no significant differences between groups were observed. Mortality in the alcohol group was 78% in the 7th week, versus 22% in the alcohol plus resveratrol group. The results of this article suggest that resveratrol reduces mortality and liver damage in mice consuming alcohol. Kasdallah-Grissa *et al.*[54] investigated whether resveratrol has a preventive effect on the main indicators of hepatic oxidative status as an expression of the cellular damage caused by free radicals, and on antioxidant defense mechanism during chronic ethanol treatment. They prescribed 5 g/kg resveratrol to Wistar rats for 6 weeks and observed that dietary supplementation with resveratrol during ethanol treatment inhibited hepatic lipid peroxidation and ameliorated SOD, GPx and CAT activities in the liver so that resveratrol could have a beneficial effect on inhibiting the oxidative damage induced by chronic ethanol administration. Jinghui *et al.*[55] investigated the effect of resveratrol (25, 50, or 100 mg/kg) on alcohol-induced hepatic injury and reported significant reduction in the concentrations of serum TNF-α, IL-6, ICAM-1 and the contents of liver NFκB p65, phosphorylating IκB-α compared with the model group consumed resveratrol for 7 days.

Hepatic oxidative damage

The effects of resveratrol on oxidative damage was examine by analyzing it's effects on sirtuins (SIRTs). SIRTs are NAD^+-dependent deacetylases that catalyze the hydrolysis of acetyl-lysine residues. They play an important role in many physiological and pathophysiological processes, such as the regulation of lifespan and the prevention of metabolic diseases. Schirmer *et al.*[56] in their study analyzed the effect of resveratrol on the gene expression levels of SIRT1, SIRT3, SIRT4, PGC1a, and NAMPT, as well as its effect on NAD^+ and NADH levels, in the liver of nonstressed or nonimpaired wild-type zebra fish. They concluded that resveratrol plays a modulatory role in the transcription of the NAMPT, SIRT3, and SIRT4 genes. Schmatz *et al.*[12] investigated the effects of resveratrol on oxidative stress parameters in liver and serum biochemical parameters of STZ-induced diabetic rats. Animals were treated with 10 or 20 mg/kg resveratrol for 30 days. They reported the elevation in serum ALT, AST and γ-glutamiltransferase (GGT) activities as well as in levels of urea, creatinine, cholesterol, and TGs observed in the nonresveratrol group were reverted to levels close to normal by the administration of resveratrol. Reduction in TBARS and elevation in activities of CAT, SOD and aminolevulinic acid dehydratase, nonprotein thiols, and Vitamin C were also seen. Another study investigated the effect of resveratrol (0.1 or 1 mg/kg) on oxidative stress and inflammatory response in the liver and spleen of STZ-induced type 1 diabetic animal models.[57] The experimental results indicated that resveratrol significantly decreased oxidative stress (superoxide anion content, protein carbonyl level and Mn-SOD expression) in both tissues and hepatic inflammation (NF-κB and IL-1β), but implicated proinflammatory potential of resveratrol in diabetic spleen (TNF-α and IL-6). Lipopolysaccharide (LPS) is a glycolipid component of the cell wall of Gram-negative bacteria inducing deleterious effects on several organs including the liver. Sebai *et al*.[58] investigated the effect of pre-treatment with resveratrol on LPS-induced hepatotoxicity in rat. Resveratrol counteracted LPS-induced lipoperoxidation and depletion of antioxidant enzyme activities as SOD and CAT but slightly GPx activity. It also abrogated LPS-induced liver and plasma nitric oxide (NO) elevation and attenuated endotoxemia-induced hepatic tissue injury. Importantly resveratrol treatment abolished LPS-induced iron sequestration from plasma to liver compartment. In another study, 1 mg/kg/day resveratrol accompanied by standard diet and HFD in Wistar rats for 30 days;[59] in HFD, resveratrol improved lipid profile and glucose level, enhanced SOD, and reduced oxidized low-density lipoprotein (ox-LDL) and hepatic oxidative stress. While in standard-fed-rats it reduced GSH-antioxidant defense system and enhanced hepatic lipid hydroperoxide. It may be concluded that resveratrol may have beneficial effects in high-fat diets (e.g., ox-LDL, decreased serum and hepatic oxidative stress), but not in standard-fed diets (effects produced include enhanced hepatic oxidative stress). Bagul *et al*.[60] compared the effect of metformin (300 mg/kg) and resveratrol (10 mg/kg) on hepatic oxidative stress in fructose-fed rats. Administration of metformin or resveratrol normalized all the altered metabolic parameters. However, a marked insulin sensitizing action was only observed in the resveratrol group. Similarly, metformin administration failed to normalize the increased TBARS levels and decreased SOD activity, while resveratrol showed a more promising effect of all oxidative stress parameters measured in this study. This study demonstrates that resveratrol is more effective than metformin in improving insulin sensitivity, and attenuating metabolic syndrome and hepatic oxidative stress in fructose-fed rats. To investigate the hepatoprotective nature of resveratrol in averting hyperglycemia-mediated oxidative stress in the hepatic tissues of STZ-nicotinamide-induced diabetic rats, 5 mg/kg resveratrol was administered for 30 days.[61] In this study, resveratrol could decline hepatic proinflammatory cytokines and hepatic lipid peroxides, hydroperoxides and protein carbonyls. In addition, diminished activities of hepatic enzymic antioxidants as well as the decreased levels of hepatic nonenzymic antioxidants of diabetic rats were reverted to near normal by resveratrol administration. Moreover, the histological and ultrastructural observations evidenced that resveratrol effectively rescues the hepatocytes from hyperglycemia-mediated oxidative damage without affecting its cellular function and structural integrity. Pyrogallol, an anti-psoriatic agent, causes hepatotoxicity in experimental animals. Resveratrol has hepatoprotective properties against pyrogallol.[62] In an animal study, administration of 10 mg/kg resveratrol modulated pyrogallol-induced changes in hepatic toxicity markers, xenobiotic metabolizing enzymes and oxidative stress. Reduction in ALT, AST, and lipid peroxidation were also seen. Farghali *et al*.[63] investigated the effects of resveratrol pretreatment on the enhancing action of D-galactosamine (D-GalN; 800 mg/kg) on (LPS; 0.5 l g/kg) inducing liver failure in rats. Reduction in ALT, AST, α-GST, TBARS, conjugated dienes and increase in CAT was seen according to resveratrol consumption. Kirimlioglu *et al*.[83] compared the antioxidant effects of resveratrol (30 mg/kg) and melatonin (10/kg) after 70% partial hepatectomy (PH). Resveratrol and melatonin suppressed PH-induced oxidative damage, attenuated proliferation, and stimulated apoptosis. When resveratrol and melatonin were compared, resveratrol showed more potent antioxidative effects and was morphologically more protective to hepatocytes. Antiproliferative effects of melatonin were more potent.[64,83] 1,2-dimethylhydrazine induced oxidative stress was suppressed by administration of resveratrol (20 mg/kg) for 30 weeks.[65] Resveratrol supplementation attenuated the liver lipid peroxidation with concomitant up-regulation of enzymic and nonenzymic antioxidant reserves.

Hepatic heat stress

The effects of dietary resveratrol on the induction of Hsp, transcription factors and antioxidative enzyme system in liver of quails under heat stress were investigated by Sahin *et al*.[66] They reported a linear increase in food intake, egg production, hepatic SOD, CAT, and GSH-Px activities as well as Nrf2 expression, but linear decrease in hepatic MDA concentrations and Hsp 70, Hsp90, and NF-κB expressions with increasing supplemental resveratrol level.

Hepatic steatosis

Xin *et al.* concluded that Alleviative effects of resveratrol on nonalcoholic fatty liver disease (NAFLD) are associated with up regulation of hepatic LDL receptor and scavenger receptor class B type I gene expressions.[67] Unexpectedly, increase in hepatic FASgene expressions was seen.[67] The effect of long-term administration (4 months) of resveratrol with high fructose (HF) diet (63%) on selected biochemical parameters and lipids content in different tissues of rats was evaluated by Kopec *et al*.[68] The concentration of lipids was significantly lower in the liver of animals fed with HFD by addition of 0.04% or 0.06% resveratrol. The concentration of TBARS (MDA equivalents) was significantly lower ($P < 0.05$) in serum of rats fed HFD with the addition of 0.04% and 0.06% of resveratrol as compared to the rodents fed with negative fructose control diet and HFD.[68] Poulsen *et al*.[69] showed that an increased number of mitochondria and, particularly, an increase in hepatic uncoupling protein 2 expression might be involved in normalizing the hepatic fat content due to resveratrol supplementation in rodents fed a high-fat diet. To analyze the influence of resveratrol on hepatic TG metabolism, 30 mg/kg resveratrol was given to Sprague–Dawley rats for 6 weeks; resveratrol decreased liver fat accumulation, increased carnitine palmitoyl transferase-Iα and acyl-coenzyme A oxydase, and decreased ACC activities.[70] Male C57BL/6J mice were fed a normal diet or a HFD (20% fat, w/w) combined with 0.005 or 0.02 % (w/w) resveratrol for 10 weeks.[71] Resveratrol significantly reduced TAG and cholesterol, as well as lipid droplet number and size. A low dose of resveratrol (0.005%) appeared to be more effective than a higher dose of resveratrol (0.02 %) for suppressing adiposity and hepatic steatosis development with a significant decrease in body weight gain, plasma TAG and total cholesterol levels. These changes were seemingly attributable to a suppression of the fatty acid (FA) synthase, glucose-6-phosphate dehydrogenase, and phosphatidate phosphohydrolase and/or an activation of FA oxidation in the liver and epididymal adipose tissue.[71] Bujanda *et al.*[72] investigated whether resveratrol decreases hepatic steatosis in an animal model of steatosis and found that Fat deposition was decreased in the resveratrol group as compared to the control group. TNF-α and MDA levels were significantly more increased in the control group. This was accompanied by increased SOD, GPx and CAT and decreased NOS in the liver of resveratrol group significantly. Glucose levels were also decreased in the group of rats given resveratrol. Resveratrol treatment led to reduced lipid synthesis and increased rates of fatty acid oxidation and prevented alcoholic liver steatosis. The protective action of resveratrol is in whole or in part mediated through the upregulation of a SIRT1-AMPK signaling system in the liver of ethanol-fed mice.[73] Rats fed a high-fat diet developed abdominal obesity, NAFLD, and insulin resistance (IR), which were markedly improved by 10 weeks of resveratrol administration. Resveratrol treatment prevented the development of abdominal obesity and IR. Chronic resveratrol administration stimulated AMPK phosphorylation and downregulated SREBP-1c and FAS gene expressions in HFD rats.[15] Resveratrol (0.04%) for 20 weeks in senescence-accelerated mouse P10 hepatocytes caused the following results;[74] lipid droplets were reduced and mitochondria were increased in number in hepatocytes. Phosphorylation of acetyl-CoA carboxylase and the expression of both the mitochondrial ATP synthase β subunit and Mn SOD2 were increased. Mitochondria, expressing more SOD2, were more tightly associated with lipid droplets, suggesting the enhancement of lipolysis through the activation of mitochondrial functions. Cathepsin D expression was less in hepatocytes but enhanced in Kupffer cells, which were increased in number and size with more numerous lysosome-related profiles.[74] The antioxidant activity of resveratrol in cholesterol-fed rats, along with its hypolipidemic effects was determined by Zhu *et al*.[75] Resveratrol significantly lowered serum lipid, hepatic cholesterol (TC), and TG levels compared to the control. Excretion of bile acids was significantly enhanced by resveratrol. The overall potential of the antioxidant system was significantly enhanced by the resveratrol as plasma and hepatic TBARS levels were lowered while serum SOD, GPx, and CAT activities were increased in nonresveratrol group. These findings suggest that resveratrol maintains an antioxidant efficacy as well as its anti-hyperlipidemic effect. Resveratrol (200 mg/kg/day) reduced body weight and liver weight gains, improved serum lipid parameters, reduced hepatic cholesterol accumulation and increased the bile acid pool size in mice fed an HFD for 8 weeks.[76] By feeding 10 or 50 ppm resveratrol in the diet to hepatoma-bearing rats for 20 days, solid tumor growth and metastasis tended to be suppressed dose-dependently.[77] Resveratrol (50 ppm) significantly suppressed the serum lipid peroxide level, indicating its antioxidative properties or those of its metabolite (s) *in vivo*. Resveratrol dose-dependently suppressed both the serum TG and very low-density lipoprotein + LDL-cholesterol levels.[77]

Liver fibrosis

Oxidative stress in liver injury is a major pathogenetic factor in progress of liver fibrosis.

Resveratrol (10 and 20 mg/kg/day) or its vehicle was administered to cirrhotic rats for 2 weeks and results were as follow:[78] Reduction in portal pressure compared to vehicle without significant changes in systemic hemodynamics. Reduction in portal pressure was associated with an improved vasodilatory response to acetylcholine, with decreased TXA2 production, increased endothelial NO, and with a significant reduction in liver fibrosis. The decrease in hepatic fibrosis was associated with a reduced collagen-1, TGF-β, NFjB mRNA expression and desmin and α-SMA protein expression.

Hong *et al*.[79] investigated the protective effects of Resveratrol on dimethylnitrosamine (DMN)-induced liver fibrosis in rats and observed that resveratrol remarkably recovered body and liver weight loss due to DMN induced liver fibrosis. Liver histology showed that Resveratrol alleviated the infiltration of inflammatory cells and fibrosis of hepatic tissue. Resveratrol decreased the level of MDA and increased the levels of GPx and SOD. Also, It significantly inhibited the mRNA expression of inflammatory mediators including inducible NO, TNF-alpha and IL-1beta. In addition, Resveratrol showed not only a reduction in mRNA expression of fibrosis-related genes such as transforming growth factor beta 1, collagen type I, and alpha-smooth muscle actin, but also a significant decrease of hydroxyproline in rats with DMN-induced liver fibrosis.

Another study[80] has shown that resveratrol (20 mg/kg daily for 4 weeks) remarkably prevented the DMN-induced loss in body and liver weight, and inhibited the elevation of serum alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin levels. Resveratrol also increased serum albumin and hepatic GSH levels and reduced the hepatic level of MDA due to its antioxidant effect. Furthermore, DMN-induced elevation of hydroxyprolinecontent was reduced in the Resveratrol treated rats, the result of which was consistent with the reduction in type I collagen mRNA expression. The reduction in hepatic stellate cell activation, as assessed by α-smooth muscle actin staining, and the reduction in transforming growth factor-β1 mRNA expression were associated with resveratrol treatment indicating the *in vivo* hepatoprotective and antifibrogenic effects of resveratrol against DMN-induced liver injury.

Lv *et al.*[81] assessed the effects of resveratrol (25, 50, or 100 mg/kg, for 6 weeks) on chronic liver fibrosis induced by CCl_4 in rats. Rats fed with 50 and 100 mg/kg of resveratrol had significant reductions in levels of the serum ALT, and liver hydroxyproline and MDA and relieving liver fibrogensis, compared with the control group.

CONCLUSION

Resveratrol can play a pivotal role in prevention and treatment of liver disorders. Previous studies confirmed its antioxidative properties in different models of hepatitis resulting in reducing of hepatic fibrosis; on the other hand, Resveratrol could reduce hepatic steatosis through modulating the insulin resistance and lipid profile in animals. These high quality preclinical studies propose the potential therapeutic implication of Resveratrol in liver disorders especially those with hepatic steatosis. Additional carefully designed, mechanistic based, laboratory, and clinical studies need to be undertaken to provide scientific evidence for the efficacy of it in treatment of liver disorders especially those with hepatic steatosis and fibrosis.

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Conflicts of interest
There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

All authors contributed in the study design, conducting the systematic review, and drafting the manuscript. All authors approved the final version for submission and take the responsibility for the manuscript content. Whereas PA had final responsibility for the decision to submit for publication.

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