Hepatoprotective Activity of Ezetimibe Against Risperidone-Induced Liver Injury in Rats

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Abstract

Background: Drug-induced hepatic injury is an unfavorable reaction to medications and/or their byproducts, which can result in ongoing harm to liver function and even death. Risperidone, the second most prescribed antipsychotic drug, has been linked to weight gain, abnormal hepatic enzyme levels, and further damage to liver cells. On the other hand, ezetimibe is an antihyperlipidemic agent that reduces serum cholesterol levels by inhibiting its absorption in the gastrointestinal tract. Additionally, it possesses antioxidant, hepatoprotective, and nephroprotective properties. **Objectives:** The purpose of this study is to evaluate the hepatoprotective and hypolipidemic effects of ezetimibe in mitigating liver damage induced by risperidone. **Materials and Methods:** A total of 24 adult male Swiss albino rats aged 6–7 weeks and weighing 170–180 g each were randomly divided into four groups, with 6 rats in each group. The first group served as a control and received vehicles only (0.5 mL of corn oil). Rats in the second group were administered risperidone alone at a dose of 2 mg/kg. In the last two groups, rats received a combination of risperidone (2 mg/kg) and ezetimibe at doses of 3 and 5 mg/kg, respectively. After sacrificing the rats, serum samples were collected to measure parameters related to lipid profile and liver enzymes. Additionally, liver tissue was immediately gathered for histopathological assessment using the NAS scoring system. **Results:** Ezetimibe exhibited marked hepatoprotective effects in rats exposed to risperidone-induced hepatic injury. This was achieved by significantly ($P < 0.05$) lowering adverse lipid profile components (TCHO, TG, LDL, and VLDL) and liver enzymes (ALT and AST), while at the same time significantly ($P < 0.05$) elevating the beneficial lipid profile (HDL). Moreover, Ezetimibe demonstrated remarkable liver protection by mitigating hepatic lobule destruction, inflammatory cell infiltration, and the presence of steatotic cells. **Conclusion:** Ezetimibe exhibited notable hepatoprotective and hypolipidemic properties in countering hepatic injury induced by risperidone.

Keywords: Ezetimibe, hepatic injury, liver enzymes, risperidone, steatosis

Introduction

Drug-induced hepatic injury refers to an adverse reaction caused by drugs or their metabolites, which can result in long-lasting harm to liver function and even death. This condition encompasses various clinical manifestations, ranging from asymptomatic features, such as alterations in hepatic enzyme levels like elevated aspartate and alanine transaminase levels, to changes in prothrombin time, albumin, direct and indirect bilirubin, as well as symptomatic acute hepatic damage, prolonged jaundice, and chronic hepatic impairment.[1] Risperidone, an atypical antipsychotic, is the second most prescribed to treat various psychiatric conditions such as bipolar disorder, schizophrenia, depression, and autism. However, its use is linked to metabolic syndrome-like effects such as weight gain, dyslipidemia, hyperglycemia due to insulin resistance, an increased risk of cardiovascular disease, hepatic enzyme abnormality, and further hepatocellular damage.[2,3] The exact cause of hepatotoxicity induced by risperidone remained uncertain. Nonetheless, several studies have suggested that the liver damage it induces

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might be linked to an indirect mechanism. This involves the development of metabolic syndrome within a few days to a week of commencing therapy, which, in turn, elevates the risk of nonalcoholic fatty liver disease.[1] The potential liver injury of risperidone could be linked to its active metabolite (9-OH-risperidone) or triggered by elevated immune cells such as eosinophilia and anti-smooth-muscle antibodies, leading to an immune allergic response and the subsequent development of hepatitis and pancreatitis.[4] Risperidone-induced hepatic injury could be linked to oxidative stress due to its pro-oxidant properties, leading to damage to lipids and proteins within the liver, and potentially causing harm to mitochondria and lysosomes.[5] Ezetimibe is an antihyperlipidemic agent that lessens serum cholesterol levels by obstructing its absorption in the gastrointestinal tract. Apart from managing dyslipidemia, it offers numerous pharmacological benefits. These include antioxidant activities that lower circulating free radicals, thereby protecting against the peroxidation of low-density lipoprotein and enhancing peripheral vascular functions.[6] Additionally, it exhibits hepatoprotective properties in animal models of liver exposed to ischemia and reperfusion, achieved through elevated glutathione levels, which possess potent antioxidant abilities.[7] Moreover, it shows nephroprotective effects by promoting autophagy and inhibiting the inflammatory response linked to the progression of chronic kidney damage.[8] Furthermore, Ezetimibe demonstrates hypoglycemic properties by improving glucose metabolism and reducing peripheral insulin resistance.[9] The objective of this study is to evaluate the potential beneficial effects of ezetimibe in protecting the liver and reducing lipid levels against liver damage induced by risperidone.

Materials and Methods

Drugs

The oral solution of Risperdal (risperidone) from Janssen-Cilag Company was acquired from a local pharmacy. The Ezetimibe powder was procured from Merck (Germany) and then formulated as a solution with a concentration of 6 mg/mL of corn oil.[10]

Animal

This study utilized a total of 24 adult male Swiss albino rats, aged 6–7 weeks and weighing 170–180 g. These rats were acquired from the Animal Resource Center, specifically from the College of Pharmacy at Kerbala University. The rats appeared healthy and were individually housed in cages within a temperature-controlled environment (25 ± 2°C) with regulated ambient moisture. The lighting followed a regular 12-h day-night cycle. Throughout the study, the rats were provided with a standard chow diet and access to water.

Experimental study

All rats were randomly divided into four groups, each containing six rats and received the drugs orally by gavage technique, as outlined below:

Control group: Rats received only vehicles, which consisted of 0.5 mL of corn oil.

Induction group: Rats received risperidone alone at a dosage of 2 mg/kg.

Ezetimibe 1 group: Rats received a combination of risperidone (2 mg/kg) and ezetimibe (3 mg/kg).

Ezetimibe 2 group: Rats received a combination of risperidone (2 mg/kg) and ezetimibe (5 mg/kg).

Every day for a span of two weeks, risperidone and ezetimibe were administered orally by using a nasopharyngeal tube.[7,11,12] The initial and final body weight of each rat was recorded during the study, while the liver weight and liver weight index were determined using the provided equation.

Liver weight index = Liver weight/body weight × 100%.[13]

At the end of the study, blood samples were gathered through heart puncture following a 15-h fasting period. The collected blood was then centrifuged at 3,000 rpm for 5 min to obtain serum for biochemical analysis. The rats were euthanized by administering an intramuscular combination of ketamine and xylazine (xylazine 3 mg/kg and ketamine 30 mg/kg) and their entire livers were subsequently excised and preserved in 10% formaldehyde for histopathological examinations.

Lipid profile and liver enzyme measurement

Total cholesterol (TCHO), triglyceride (TG), high-density lipoprotein (HDL), aspartate transaminase (AST), and alanine transaminase (ALT) were measured by using commercial diagnostic kits. Very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) were mathematically measured with aid of the Friedewald equation.

Histopathological examination

A 5 mm section of liver tissue from each rat was incisioned, kept in 10% buffer formaldehyde, and embedded in paraffin using the standard method. The blocks of tissue-paraffin subjected subsequently partition to make sequential levels, and then stained with hematoxylin and eosin. They were examined under a light microscope and scored using nonalcoholic steatohepatitis (NAS) system to evaluate the pathological alterations on a scale as shown in Table 1.[14]

Statistical analysis

Statistical Package for Social Sciences (SPSS 22) was employed to conduct the statistical analysis. The numerical data was presented using the mean and

standard error of the mean (mean ± SE). To compare the body weight of all groups beginning and at the end of the study, a paired *t* test was employed. Additionally, the one-way ANOVA test, along with *post hoc* – LSD tests, was utilized to compare between the study groups. Statistical significance was established for P value < 0.05.[15]

Ethical approval

All procedures and protocols adhered to the ethical guidelines set by the Ethical Committee of Kerbala University–College of Pharmacy, with the project being assigned No. 2022An.36.

Result

The body weight, liver weight, and liver weight index

There were no significant differences in the initial body weights among the study groups at $P > 0.05$. However, the final body weight of rats increased significantly in comparison to their respective initial body weights in all study groups ($P < 0.05$). Comparatively, the induction group exhibited significantly higher final body weight, liver weight, and liver weight index compared to the other study groups ($P < 0.05$). On the other hand, no significant differences were observed among the ezetimibe 1, ezetimibe 2, and control groups concerning final body weight, liver weight, and liver weight index ($P > 0.05$), as indicated in Table 2.

Table 1: Nonalcoholic steatohepatitis score system[14]

Hepatic steatosis	Intralobular inflammation	Balloon degeneration
0: <5%	0: Nothing	0: Nothing
1: 5–33%	1: <2	1: Little
2: 34–66%	2: 2–4	2: Large
3: >66%	3: >4	

Table 2: Body weight, liver weight, and liver weight index of each group (mean ± SE)

Groups	Initial weight (g)	Final weight (g)	Liver weight (g)	Liver index (%)
Control	178.17 ± 3.24	185.83 ± 3.28	6.8 ± 0.23	3.52 ± 0.11
Induction	174.17 ± 2.71	249.67 ± 5.52	11.39 ± 0.63*	4.58 ± 0.30*
Ezetimibe 1	179.83 ± 2.68	188.50 ± 2.62	6.57 ± 0.43	3.36 ± 0.21
Ezetimibe 2	176.83 ± 4.09	188.00 ± 3.12	7.13 ± 0.23	3.59 ± 0.15

*Significant effect ($P < 0.05$) compared to other groups

Effects of ezetimibe on lipid profile

Risperidone led to a significant occurrence of dyslipidemia, characterized by increased levels of TCHO, TG, LDL, and VLDL, along with decreased HDL levels compared to the control group at $P < 0.05$. Both strengths of ezetimibe resulted in a significant reduction in TCHO, TG, LDL, and VLDL levels and an elevation in HDL levels compared to the induction group at $P < 0.05$. In particular, the ezetimibe 2 group exhibited significantly lower TCHO and TG levels when compared to both the ezetimibe 1 and control groups at $P < 0.05$, as indicated in Table 3 and Figure 1.

Effects of ezetimibe on liver enzymes

The liver enzymes (ALT and AST) of rats in the induction group showed a significant increase compared to the other study groups at a significance level of $P < 0.05$. However, there were no significant differences were observed among the ezetimibe 1, ezetimibe 2, and control groups concerning liver enzymes ($P > 0.05$), as presented in Table 4 and Figure 2.

Effects of ezetimibe on histopathological features of liver

The liver structures of rats in the control group exhibited a uniform arrangement of hepatocytes with well-defined hepatic lobules and centrally located nuclei within the cells, as depicted in Figure 3. In contrast, treatment with risperidone resulted in a notable induction of hepatocellular injury, characterized by the destruction of hepatic lobules, congestion, infiltration of inflammatory cells, and hepatocytes exhibiting a ballooned appearance, along with a substantial number of hepatocytes suffering from steatosis, as shown in Figure 4. Conversely, in the ezetimibe 1 group, the administration of ezetimibe led to a significant reduction in the destruction of hepatic lobules, infiltration of inflammatory cells, and the number of steatotic cells, as illustrated in Figure 5. Similarly, in the ezetimibe 2 group, most hepatocytes appeared normal, with only a few steatotic cells observed, as demonstrated in Figure 6. Importantly, there were no significant

Table 3: Lipid profile of each group (mean ± SE)

Groups	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	High-density lipoprotein (mg/dL)	Low-density lipoprotein (mg/dL)	Very low-density lipoprotein (mg/dL)
Control	94.17 ± 4.73	208.50 ± 12.52	36.67 ± 1.26	16.33 ± 1.78	41.70 ± 2.50
Induction	116.83 ± 5.13*	252.50 ± 12.88*	26.33 ± 2.54*	25.5 ± 2.19*	50.5 ± 2.58*
Ezetimibe 1	89.83 ± 4.71	212.67 ± 16.17	37.83 ± 3.44	14.5 ± 1.52	42.53 ± 2.23
Ezetimibe 2	64.5 ± 4.09#	158.00 ± 4.55#	43.33 ± 4.10	13.67 ± 1.52	31.60 ± 0.91

*Significant effect ($P < 0.05$) compared to other groups

#Significant effect ($P < 0.05$) compared to control and ezetimibe 1 groups

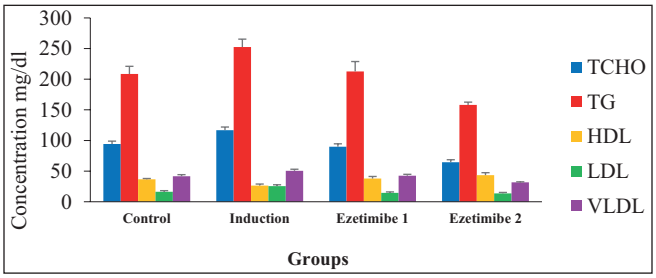

Figure 1: The concentration of lipids in each group. TCHO, total concentration; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein

Table 4: Liver enzymes of each group (mean ± SE)

Groups	Alanine transaminase (mg/dL)	Aspartate aminotransferase (mg/dL)
Control	42.17 ± 3.11	85.17 ± 4.35
Induction	67.83 ± 5.59*	120.17 ± 7.68*
Ezetimibe 1	49.50 ± 0.62	96.83 ± 1.30
Ezetimibe 2	47.67 ± 1.99	93.00 ± 0.37

*Significant effect ($P < 0.05$) compared to other groups

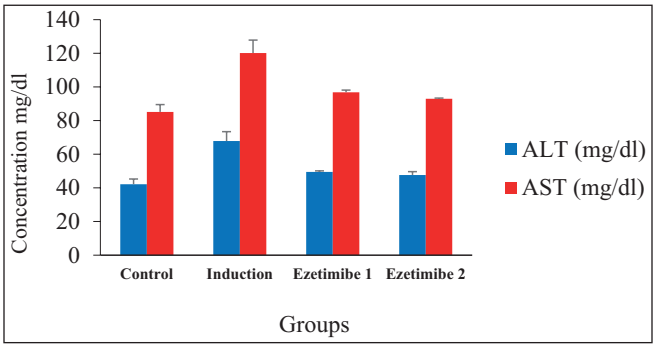

Figure 2: Concentration of liver enzymes in each group. ALT, alanine transaminase; AST, aspartate transferase

differences between the ezetimibe 1 and ezetimibe 2 groups concerning the improvement of liver histopathological changes ($P > 0.05$), as presented in Table 4.

Table 5 represents the comparison between the ezetimibe 1 and ezetimibe 2 groups concerning the Nonalcoholic steatohepatitis score changes.

Discussion

The occurrence of drug-induced liver injury caused by psychotropic medications has become a major health concern. It can result in various clinical manifestations, including acute liver failure. This issue has been on the rise globally, attributable to several factors such as the widespread and prolonged usage of these drugs, the prevalence of psychiatric and metabolic disorders, and the frequent administration of multiple medications to psychiatric patients.[1] Risperidone's long-term utilization as an antipsychotic agent has been limited due to prevalent adverse effects, namely obesity, dyslipidemia, and hepatotoxicity.[16]

In this research, it was observed that the body weight of rats in all the study groups exhibited a significant increase, and the administration of risperidone notably led to weight gain, along with an increase in both liver weight and liver weight index. These findings are consistent with prior studies indicating that, within just 12 days of commencing treatment, risperidone significantly enhanced food intake and promoted body weight gain in rats.[17] Ezetimibe effectively preserved normal body weight, liver weight, and liver weight index when compared to the control group. Moreover, it demonstrated the ability to reduce total body weight significantly by restoring lipid dysregulation after meals and altering the function of fat tissue hormones.[18] According to another study, obese rats treated with ezetimibe experienced a decrease in body weight and an improvement in insulin resistance, hyperlipidemia, and hepatic steatosis.[19]

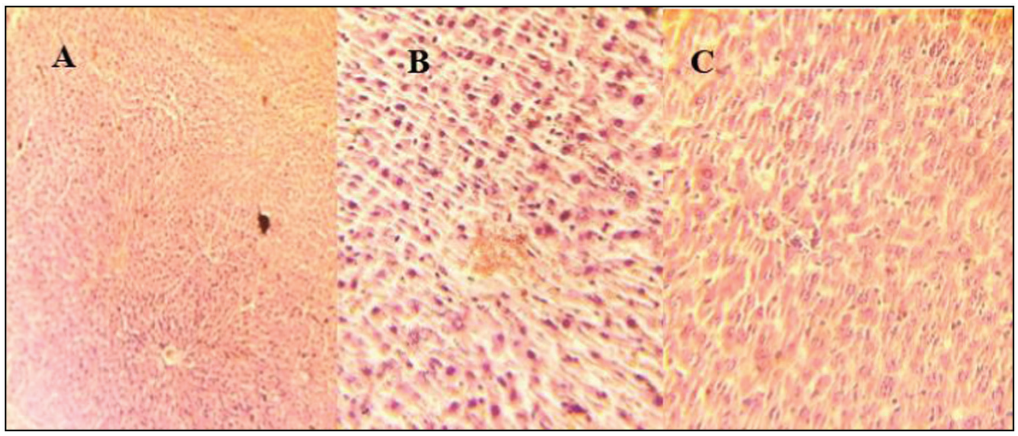

Figure 3: Liver section from rats of control group showing uniformity arrangement of the hepatocytes with right hepatic lobules and central nucleus in the cells (H&E (A) 10X, and (B, C) 40X)

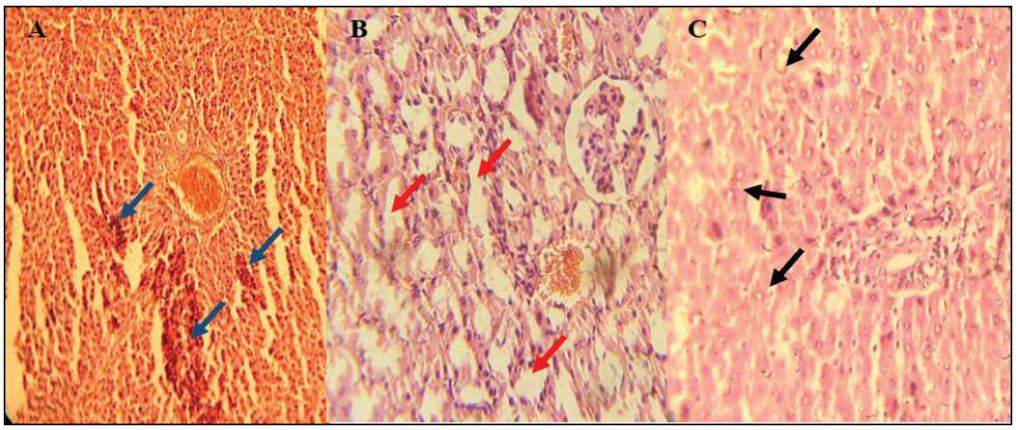

Figure 4: Liver section from rats of induction group showing balloon degeneration (black arrows), congestion and infiltration of inflammatory cells (blue arrows), and high number of steatotic hepatocytes (red arrows) (H&E (A) 10X, and (B, C) 40X)

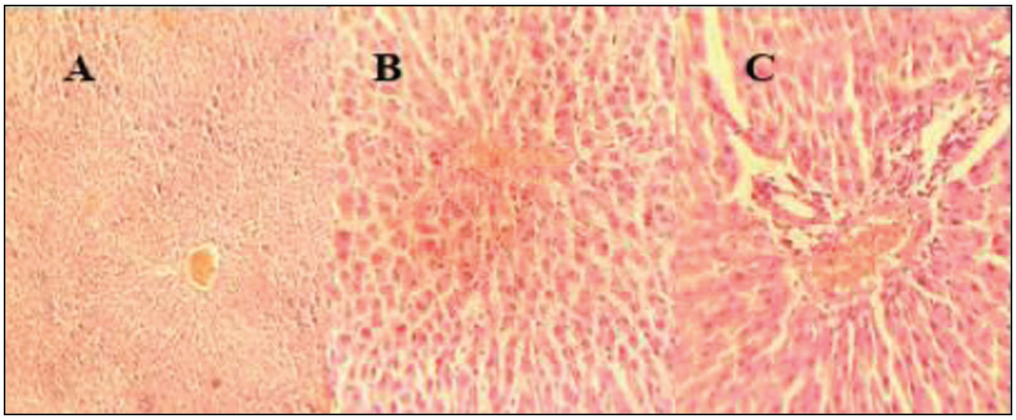

Figure 5: Liver section from rats of ezetimibe 1 group showing low destruction of hepatic lobules, some inflammatory cells, and few steatotic cells (H&E (A) 10X, and (B, C) 40X)

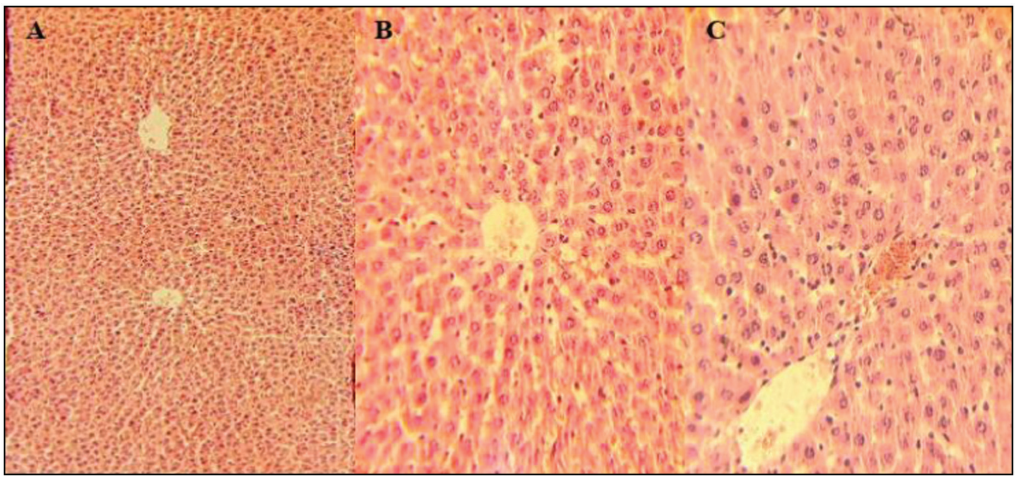

Figure 6: Liver section from rats of ezetimibe 2 group showing normal arrangement of hepatocytes and presence of very few steatotic cells (H&E (A) 10X, and (B, C) 40X)

In this study, it was observed that risperidone had a notable impact on dyslipidemia, leading to increased levels of TCHO, TG, LDL, and VLDL, while reducing HDL when compared to the control group. Rats treated with risperidone experienced higher fasting triglyceride levels and increased white adipose tissue, attributed to the accumulation of TG. Additionally, the risperidone-treated rats showed elevated fasting insulin levels due to insulin

Table 5: Nonalcoholic steatohepatitis score of each group (mean ± SE)

Groups	Nonalcoholic steatohepatitis score
Control Induction	0.67 ± 0.21
Ezetimibe 1	6.67 ± 0.49*
Ezetimibe 2	2.33 ± 0.49**
	2.00 ± 0.26**

*Significant effect ($P < 0.05$) compared to other groups

**Significant effect ($P < 0.05$) compared to control group

resistance and impaired glucose responses.[20] Compared to the control group, ezetimibe effectively maintained normolipidemic levels. It demonstrated the capacity to reduce fasting plasma cholesterol and TG to baseline levels by decreasing fast VLDL and LDL, which in turn limited cholesterol availability to the liver. As a result, ezetimibe promoted the production of HDL.[21] different study unveiled that administering just one dose of ezetimibe could potentially lead to a reduction in postprandial chylomicrons and chylomicron remnants' cholesterol levels, while leaving the chylomicron triglyceride content unaffected.[22]

In this study, risperidone significantly increased liver enzyme (ALT, AST) in comparison with the control group. The administration of Risperidone may lead to fat build-up in the liver, potentially resulting in liver injury and elevated levels of liver enzymes, particularly ALT and AST,[23] while ezetimibe significantly maintained the normal level of liver enzyme when compared with the control group. Ezetimibe has been shown to enhance liver steatosis by reducing lipid absorption, thereby decreasing the need for lipoprotein production. Furthermore, Ezetimibe has demonstrated its ability to protect against liver steatosis by inhibiting the production of transforming growth factor β, which originates from Kupffer cells and other inflammatory cells.[24] Different research conducted an exploration into the functions of ezetimibe in nonalcoholic fatty liver disease (NAFLD). It was observed that ezetimibe increased the expression of microsomal triglyceride transfer protein (MTP) while also preventing its degradation. Consequently, this led to a decrease in hepatic lipid production and facilitated the removal of lipids from the liver, ultimately inhibiting the progression of NAFLD.[25] Ezetimibe might exhibit antioxidant properties in cases of liver subjected to ischemia-perfusion injury by elevating glutathione levels and reducing glutathione peroxidase activity, all while having no impact on liver enzyme levels.[7]

This study observed that risperidone caused notable hepatic damage, which included balloon degeneration, infiltration of inflammatory cells, and steatosis (fat accumulation) in hepatocytes. Risperidone was found to increase the likelihood of obesity, leading to fat accumulation in the abdominal region and contributing to the development of fatty liver disease, glucose intolerance, and insulin resistance. Consequently, the liver was affected to varying degrees, ranging from mild steatosis to more severe hepatosteatosis, and potentially culminating in cryptogenic cirrhosis.[16] Ezetimibe demonstrated a significant protective effect on the liver, as evidenced by its ability to reduce the destruction of hepatic lobules, infiltration of inflammatory cells, and the presence of steatotic cells, in comparison to the control group. Ezetimibe exhibited the capacity to lower serum cholesterol levels, reduce fat accumulation in the liver, and improve hepatic insulin resistance.[26] During a span of 4 weeks, administering ezetimibe in varying doses resulted in a notable decrease in plasma alanine aminotransferase activity and hepatomegaly in diet-induced obese mice. This reduction was accomplished by lowering hepatic triglyceride, cholesteryl ester, and free cholesterol levels, indicating a dose-dependent relationship.[27] It provided protection to the liver from steatosis by reducing the hepatic mRNA expression essential for transcribing genes responsible for hepatic fatty acid synthesis, such as the acetyl-CoA carboxylase alpha (ACC1) gene and stearoyl-CoA desaturase (Scd1) gene.[28]

Conclusion

In conclusion, ezetimibe exhibited notable hepatoprotective and hypolipidemic properties in the context of hepatic injury induced by risperidone.

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Conflicts of interest

There are no conflicts of interest.

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