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The Effect of Atorvastatin and Different Doses of Hesperidin on Hepatotoxicity

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ABSTRACT

Background and Objective: Statin-induced hepatotoxicity has a serious impact on elderly patients and high-risk individuals. Therefore, any sign of liver injury should be carefully monitored and evaluated, especially given the high number of patients who receive statins as part of their medication. The aim of this study is to investigate the possible hepatoprotective effects of different doses of hesperidin against atorvastatin-induced hepatotoxicity.

Methods: In this experimental study, 30 male Wistar rats, aged 10-12 weeks, were divided into five groups of six: 1: saline (control), 2: recipients of 80 mg/kg/day atorvastatin, 3: recipients of 80 mg/kg/day atorvastatin + 50 mg/kg/day hesperidin, 4: recipients of 80 mg/kg/day atorvastatin + 100 mg/kg/day hesperidin, 5: recipients of 80 mg/kg/day atorvastatin + 200 mg/kg/day hesperidin. All animals received their drugs by oral gavage. The animals were then sacrificed and the liver of each animal was harvested for further gene studies, and a small portion was collected in Eppendorf Transwells to measure and compare the expression of BAX, BCL-2 and TLR-4 genes.

Findings: The results showed that the expression of Bax (proapoptotic gene) in group 2 (recipients of 80 mg/kg/day atorvastatin) (1.81±0.48) significantly increased compared to the other groups ($p<0.05$). However, the expression of Bcl-2 (anti-apoptotic gene) showed a reverse trend in group 2 compared to the control group (0.29±0.25 vs. 0.43±1.00) ($p<0.05$). Moreover, the expression of TLR-4 gene in group 2 significantly increased compared to the other groups (1.61±0.36 vs. 0.15±0.00) ($p<0.05$).

Conclusion: The results of the study showed that hesperidin consumption can prevent liver damage caused by high doses of atorvastatin.

Keywords: *Atorvastatin, Hesperidin, Bax, Bcl-2, TLR-4.*

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Introduction

The liver is one of the body's most vital organs, playing a key role in metabolism, immune system support, and detoxification. Although these functions are essential, they also render the liver susceptible to various problems, including injury from the medications and chemicals that it detoxifies (1, 2). Therefore, drug-related side effects represent a major threat to the liver and may even result in death. These adverse effects can be caused either by the drug itself or by its metabolites, leading to a range of clinical outcomes, including idiosyncratic reactions (3).

Atorvastatin is a widely prescribed lipid-lowering agent that exerts its therapeutic effect through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (4). Although this mechanism provides cardiovascular protection, it may also give rise to adverse effects, including diabetes and muscle-related complications (5). Elevated lipid levels are associated with an increased risk of cardiovascular disease (CVD), which remains one of the leading causes of mortality worldwide. This link between CVD and elevated cholesterol is largely attributable to plaque formation within the coronary arteries, which may lead to various ischemic heart conditions. Prior to the advent of statin therapy, dietary fat restriction was the primary strategy recommended for managing this risk (6, 7).

Epidemiological data have estimated that every 1 mmol/L reduction in LDL cholesterol corresponds to a 22% decrease in the annual rate of major vascular events. Consistent with this finding, clinical research has demonstrated that a daily dose of 40 mg of atorvastatin achieves an approximate 50% reduction in LDL levels. This response appears to be largely independent of baseline patient characteristics, and dose-response analyses have further shown that, on average, doubling the dose of any statin results in an additional 6 percentage point reduction in LDL cholesterol (8).

Atorvastatin offers cardiovascular protection not only through cholesterol reduction but also via additional pleiotropic effects, including reduction of LDL-cholesterol oxidation, stabilization of atheroma plaques, inhibition of endothelial dysfunction, and decreased platelet activity (9). Despite the remarkable benefits of atorvastatin for patients at risk of cardiovascular disease, it is associated with a range of potential adverse effects, including hemorrhagic stroke, memory impairment, increased cataract formation, and possible renal dysfunction. Other side effects attributed to statins include neuropathy, sleep disturbances, suicidal ideation, and diabetes mellitus (10).

On the other hand, statins in general have been reported to be among the most frequently implicated drugs in chronic liver injury. Atorvastatin appears to be the most commonly associated statin; however, hepatotoxicity has also been documented with simvastatin, and to a lesser extent, with fluvastatin, pravastatin, and rosuvastatin (10, 11). Hesperidin, a compound found in citrus fruits, is both affordable and offers a wide range of health benefits. Deficiency of hesperidin has been associated with abnormal capillary permeability, limb pain, weakness, and leg cramps. Furthermore, hesperidin supplementation has been shown to help reduce edema, including excessive leg swelling caused by fluid retention (12).

Following clinical studies, hesperidin became available on the market not only as a dietary supplement but also as a component of Daflon tablets, which consist of 90% diosmin and 10% hesperidin. This formulation is primarily used for the treatment of hemorrhoids, owing to its ability to alleviate symptoms such as pain and bleeding. The Bcl-2 family (B cell lymphoma protein 2) consists of both pro-apoptotic and anti-apoptotic proteins that regulate cell death, thereby preventing uncontrolled cell death that could threaten life. Bcl-2 is a well-known anti-apoptotic member, while Bax (Bcl-2 associated X protein) is a pro-apoptotic member (13). These proteins are activated by various intracellular and extracellular stimuli, rendering them sensitive to environmental changes and subject to tight physiological regulation (14).

Consequently, the Bcl-2 family has emerged as a promising therapeutic target in oncology (15) and also serves as a measurable marker for assessing whether cells are undergoing apoptosis. Therefore, Bcl-2 and Bax gene expression was measured in this study to determine whether the medications induced apoptosis. TLR4 is expressed within the liver on various cell types, including Kupffer cells and hepatocytes (16), and its stimulation leads to the activation of a pro-inflammatory response (17). Hesperidin has also demonstrated hepatoprotective effects against other agents in previous studies, including ethanol (18), carbon tetrachloride (19), mercury (20), and doxorubicin (21).

Research has shown that this compound exhibits antiviral and antibacterial activity, both as a monotherapy and in combination with other agents, and may also modulate immune function. However, its most extensively investigated property is its anti-inflammatory effect, with studies demonstrating efficacy in managing allergic reactions and reducing local edema at inflammatory sites. These observations have given rise to the hypothesis that its mechanism may involve histamine reduction, as well as antioxidant activity through free radical scavenging (22). The aim of the present study was to evaluate the potential hepatoprotective effects of various doses of hesperidin against atorvastatin-induced hepatotoxicity.

Methods

In this experimental study, 30 male Wistar rats, aged 10-12 weeks and weighing approximately 230 grams, were used. They were housed in the animal facility of Mustansiriyah University under standardized conditions (23, 24), including controlled temperature, humidity, and a 12-hour light/dark cycle. Pellet diet was provided for nourishment, along with unlimited access to tap water. The experimental procedures were reviewed and approved by the Mustansiriyah University College of Pharmacy Animal Ethics Committee (Ref. No. 150/23.10.2023). The rats were divided into five groups (Figure 1).

Atorvastatin and Hesperidin: Atorvastatin (purchased from AstraZeneca, Germany) and hesperidin (purchased from China) were both dissolved in DMSO. The required doses were calculated based on the experimental groups and the body weight of each rat, and were then administered accordingly.

Study design: Thirty Wistar male rats were randomly and equally divided into five groups, each group containing six rats, and received treatment as follows:

Group 1 (negative control group): received normal saline via oral gavage for 20 days.

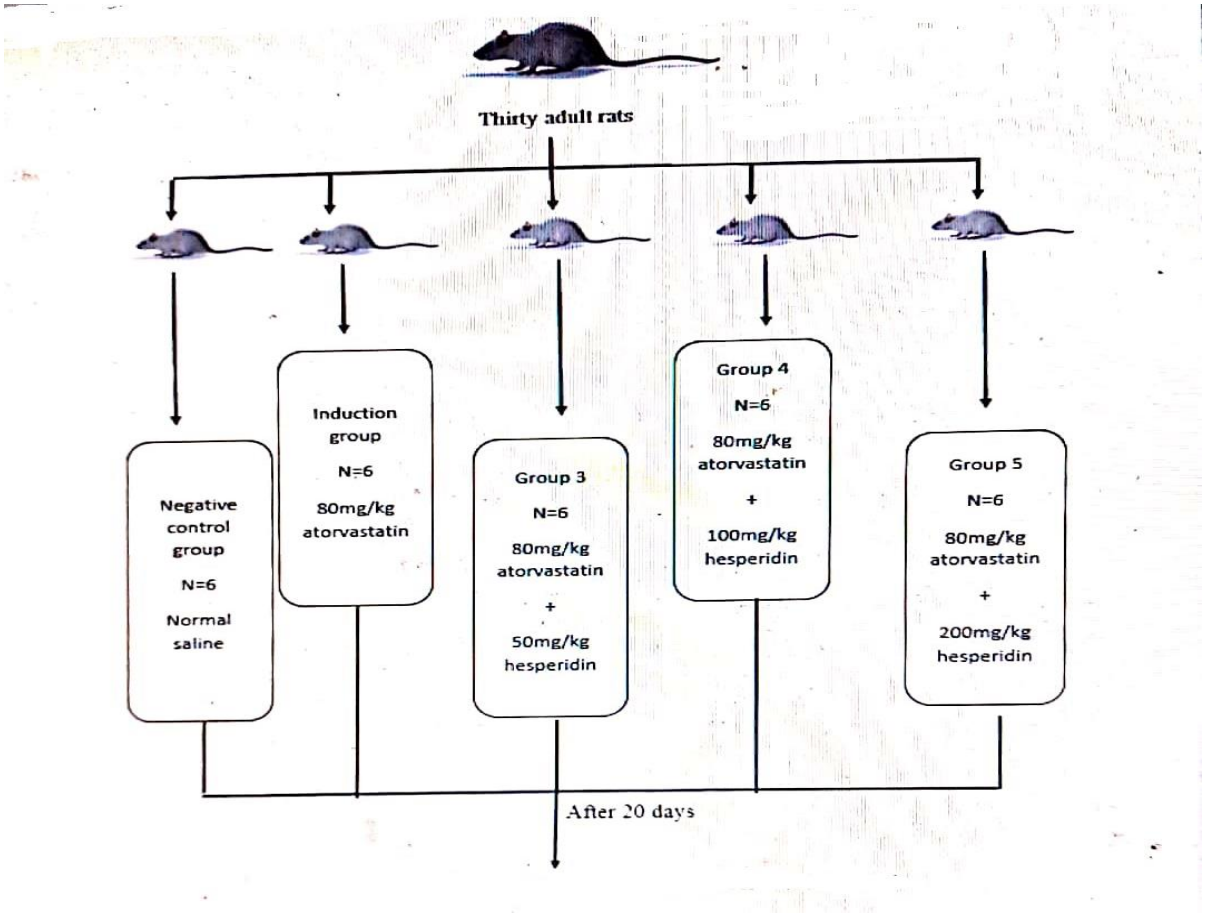
Group 2 (positive control group): received a toxic dose of 80 mg/kg of atorvastatin to induce hepatotoxicity. The doses were administered via oral gavage for 20 days.

Group 3: received a toxic dose of 80 mg/kg of atorvastatin together with a low dose of 50 mg/kg of hesperidin. The doses were administered via oral gavage for 20 days.

Group 4: received a toxic dose of 80 mg/kg of atorvastatin together with a moderate dose of 100 mg/kg of hesperidin. The doses were administered via oral gavage for 20 days.

Group 5: received a toxic dose of 80 mg/kg of atorvastatin together with a high dose of 200 mg/kg of hesperidin. The doses were administered via oral gavage for 20 days.

The animals were then sacrificed, and the liver of each rat was harvested for further gene expression studies (Table 1). A small portion of each liver sample was immersed in TransZol solution in Eppendorf tubes for subsequent measurement and comparison of Bax, Bcl-2, and TLR-4 gene expression.



After 20 days, blood samples were collected, serum was separated, and the liver was harvested.



Figure 1. Division of rats into 5 study groups. All animals received their drugs by oral gavage.

Table 1. Primer sequences used in this study

Primer	Sequence 5′→3′ direction
Bax	
Forward	AGGATCGAGCAGAGAGGATG
Reverse	GTCCAGTTCATCGCCAATTC
Bcl-2	
Forward	GGTGGTGGAGGAACTCTTCA
Reverse	ATGCCGGTTCAGGTACTCAG
TLR 4	
Forward	CAGGGAATTAGGCTCCATGA
Reverse	TCCATGACAGAACGGTCAAA
β-actin	
Forward	CTATCGGCAATGAGCGGTTCC
Reverse	TGTGTTGGCATAGAGGTCTTTACG

Total RNA was extracted from liver tissue using TRIzol reagent, followed by phase separation and ethanol precipitation. cDNA synthesis was carried out using EasyScript® reverse transcriptase, and primers were prepared with nuclease-free water. β-actin was used as the housekeeping gene, and primer sequences were designed using Primer-BLAST (NCBI). Quantitative PCR was performed using TransStart® qPCR according to the manufacturer's protocol (25).

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) software. All results were expressed as mean±standard error of the mean (SEM). Intergroup comparisons were performed using Student's t-test and one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. Statistical significance was set at $p<0.05$.

Results

In Group 2, which received 80 mg/kg of atorvastatin (0.29±0.25-fold), the mean tissue Bcl-2 expression was significantly lower compared to Group 1 (normal saline, 1.00±0.43-fold) ($p<0.05$). The addition of hesperidin produced varying effects on Bcl-2 expression. The combination of atorvastatin (80 mg/kg) with hesperidin (50 mg/kg) (0.88±0.67-fold) did not show a significant change compared to Group 2. In contrast, atorvastatin (80 mg/kg) with hesperidin (100 mg/kg) (7.17±1.12-fold) resulted in significantly higher Bcl-2 expression compared to Group 2 ($p<0.05$). However, the combination with the highest dose of hesperidin (200 mg/kg) (1.91±1.24-fold) did not demonstrate a significant change compared to Group 2 ($p<0.05$) (Table 2, Figure 2).

Table 2. Effect of atorvastatin and hesperidin on Bcl-2 expression in the male rat model. Data are presented as mean fold change±standard error of the mean (SEM)

Group	Gene expression (fold)
Control group given normal saline	1.00±0.43 a
Induction group (80 mg/kg of atorvastatin)	0.29±0.25 b
80 mg/kg atorvastatin + 50 mg/kg hesperidin	0.88±0.67 b
80 mg/kg atorvastatin + 100 mg/kg hesperidin	7.17±1.12 c
80 mg/kg atorvastatin + 200 mg/kg of hesperidin	1.91±1.24 b

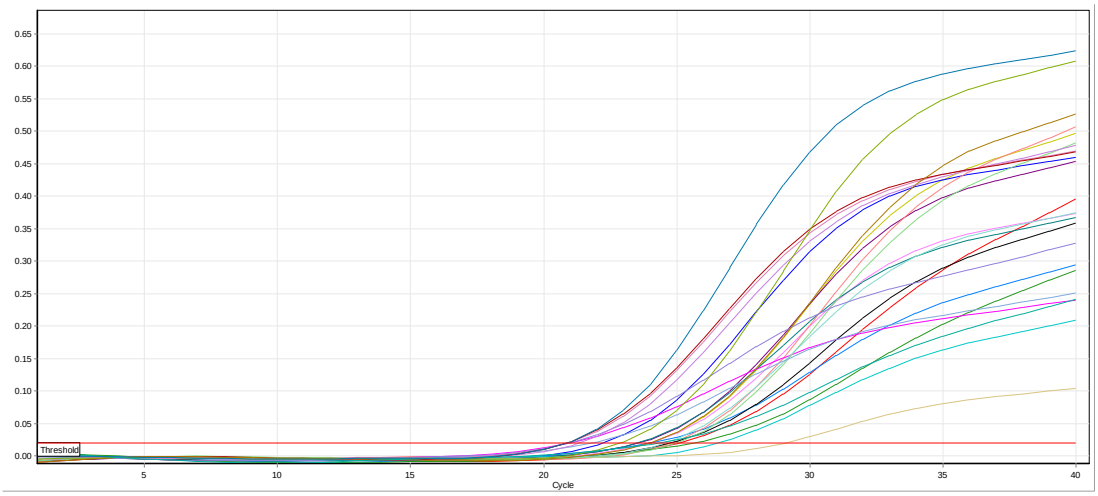


Figure 2. Bcl-2 amplification plots by RT-PCR. Samples in the figure included all study groups (n=30), and the image was captured directly from the Qiagen Rotor-Gene PCR instrument

For Bax gene expression, Group 2 (atorvastatin 80 mg/kg) showed a mean fold change of 1.81±0.48, which was significantly higher than that of Group 1 (saline, 1.00±0.15) ($p<0.05$). The addition of hesperidin resulted in a dose-dependent reduction in Bax expression. The combination of atorvastatin with 50 mg/kg hesperidin yielded a mean fold change of 0.67±0.19, which was significantly lower than atorvastatin alone ($p<0.05$). Similarly, atorvastatin with 100 mg/kg hesperidin (0.34±0.12) also showed a significantly lower mean Bax fold change compared to atorvastatin alone ($p<0.05$). The lowest mean Bax expression was observed in the group receiving atorvastatin with 200 mg/kg hesperidin (0.07±0.04), which was significantly lower than atorvastatin alone (1.81±0.48) ($p<0.05$) (Table 3, Figure 3). RT-PCR amplification plots for Bax are shown in Figure 4, with samples from all study groups (n=30), and the image was captured directly from the Qiagen Rotor-Gene PCR instrument.

Table 3. Effect of atorvastatin and hesperidin on Bax expression in the male rat model. Data are presented as mean±standard error (SE)

Group	Gene expression (fold)
Control group given normal saline	1.00±0.15[a]
Induction group given 80 mg/kg of atorvastatin	1.81±0.48[b]
80 mg/kg atorvastatin + 50 mg/kg hesperidin	0.67±0.19[c]
80 mg/kg atorvastatin + 100 mg/kg hesperidin	0.34±0.12[d]
80 mg/kg atorvastatin + 200 mg/kg of hesperidin	0.07±0.04[e]

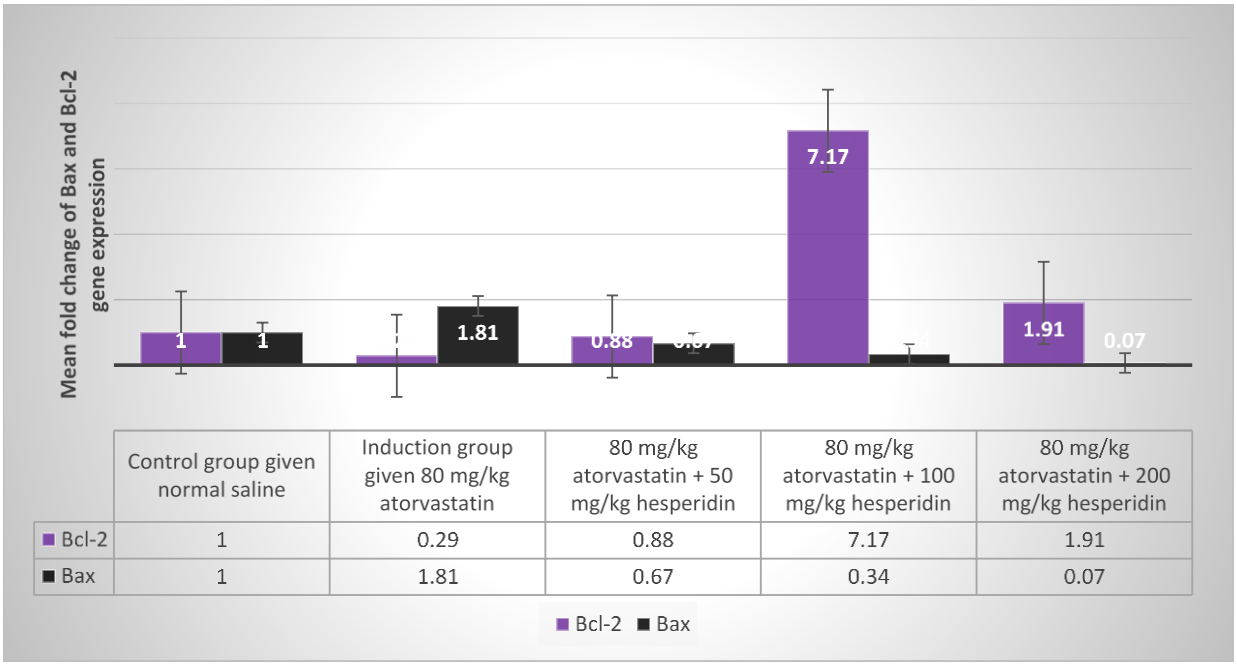


Figure 3. Effects of atorvastatin and different doses of hesperidin on Bcl-2 and Bax gene expression.
Data are presented as mean fold change.

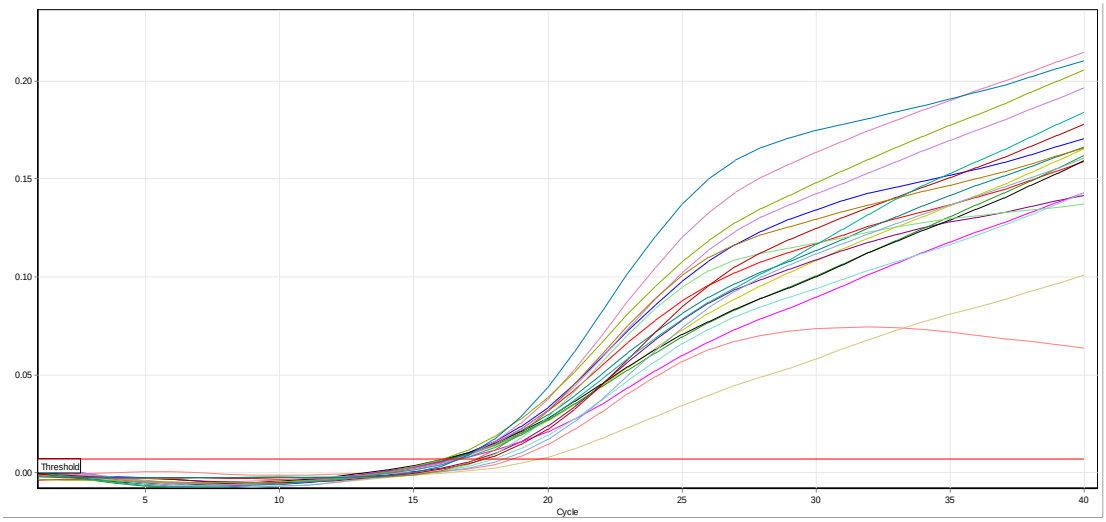


Figure 4. Bax amplification plots obtained by RT-PCR. The figure includes samples from all study groups (n=30), and the image was captured directly from the Qiagen Rotor-Gene PCR instrument.

For TLR-4 gene expression, Group 2 (atorvastatin 80 mg/kg) showed a mean fold change of 1.61±0.36, which was significantly higher than that of Group 1 (saline, 1.00±0.15, $p<0.05$) (Figure 5). The addition of hesperidin produced varying effects on TLR-4 expression. The combination of atorvastatin with 50 mg/kg hesperidin (1.33±0.55-fold) did not result in a significant change compared to atorvastatin alone. Similarly, atorvastatin with 100 mg/kg hesperidin (0.44 ± 0.40-fold) also showed no significant difference compared to atorvastatin alone ($p<0.05$). However, the combination of atorvastatin (80 mg/kg) with the highest dose of hesperidin (200 mg/kg) (0.13±0.01-fold) resulted in a significantly lower TLR-4 expression compared to atorvastatin alone (1.61±0.36-fold, $p<0.05$) (Table 4, Figure 6).

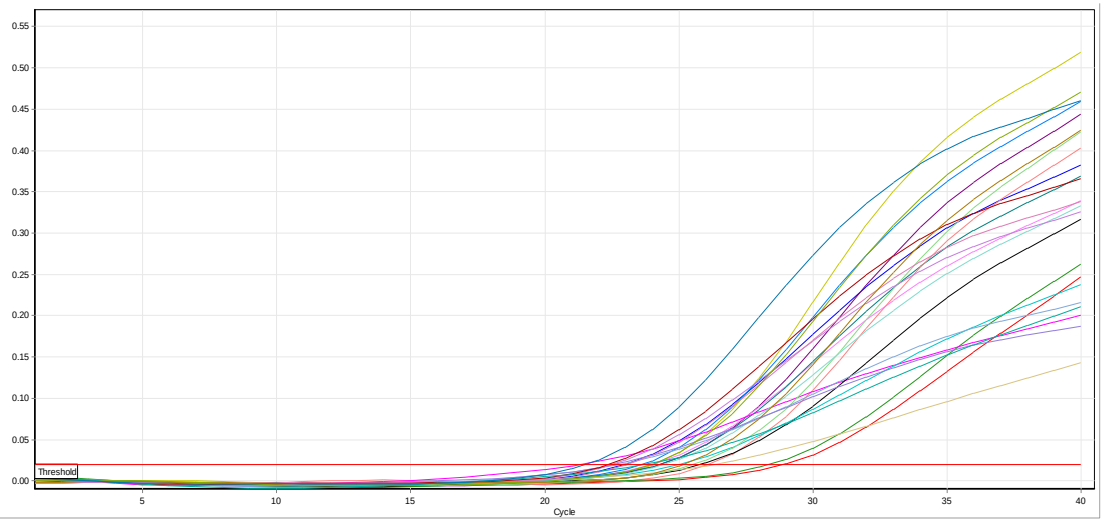


Figure 5. TLR-4 amplification plots obtained by RT-PCR. The figure includes samples from all study groups (n=30), and the image was captured directly from the Qiagen Rotor-Gene PCR instrument.

Table 4. Effect of atorvastatin and hesperidin on TLR4 expression in the male rat model

Group	Gene expression (fold)
Control group given normal saline	1.00±0.15[a]
Induction group given 80 mg/kg of atorvastatin	1.61±0.36[b]
80 mg/kg atorvastatin + 50 mg/kg hesperidin	1.33±0.55 [b]
80 mg/kg atorvastatin + 100 mg/kg hesperidin	0.44±0.40[b]
80 mg/kg atorvastatin + 200 mg/kg of hesperidin	0.13±0.01[c]

Results were expressed as Mean±SE.

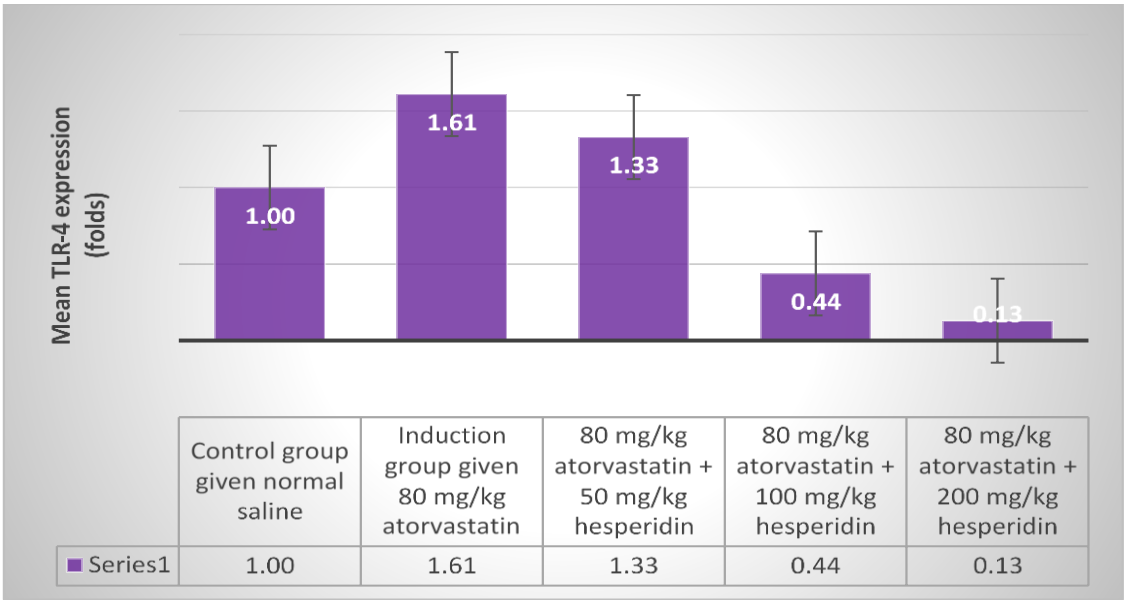


Figure 6. Effects of atorvastatin and different doses of hesperidin on TLR-4 expression. Data are presented as Mean±SD.

Discussion

The results demonstrated a marked up-regulation of the pro-apoptotic gene Bax in the atorvastatin-treated group (80 mg/kg), with expression levels nearly doubling those of the control group. Concurrently, expression of the anti-apoptotic gene Bcl-2 was down-regulated to less than half of control levels. These findings indicate that 80 mg/kg of atorvastatin triggered hepatocyte apoptosis. The activation of the programmed cell death pathway may have been initiated by cellular leakage, membrane permeability damage, or oxidative stress.

The present findings regarding Bcl-2 expression are in agreement with those of an in vitro study by Radha et al. on vascular smooth muscle cells (26). However, they contradict the results of an in vivo investigation by Blanco-Colio et al. (27), suggesting that the effects of atorvastatin on Bcl-2 expression may be tissue-specific and context-dependent.

The Bax findings are inconsistent with those of some studies, including an in vivo study published in 2020 (28), but are consistent with a study from 2009 (29). These discrepancies may again be explained by different effects of atorvastatin on different tissues.

In the other treatment groups, varying gene expression levels were observed. Bax was consistently down-regulated with increasing doses of hesperidin, suggesting a dose-dependent reduction in cell death. Notably, the combination of 80 mg/kg atorvastatin with 100 mg/kg hesperidin resulted in a 7-fold up-regulation of Bcl-2 compared to the control group, indicating that this group received the greatest protection against apoptosis. This suggests that the anti-inflammatory and antioxidant properties of hesperidin provided sufficient cellular protection to restore balance and prevent cell death. These findings regarding the protective effect of hesperidin were expected, as they are consistent with previous research conducted on multiple occasions, including a study on a male rat model in 2020 that reported a significant increase in Bcl-2 levels and a decrease in Bax levels following hesperidin exposure. The authors attributed this effect to the antioxidant properties of hesperidin (30).

The present findings revealed a significant up-regulation of TLR4 expression following atorvastatin administration, along with a protective effect conferred by hesperidin. While some earlier investigations have reported that atorvastatin down-regulates TLR4 (31), conflicting data exist in the literature suggesting the opposite effect (32). These divergent observations may be attributable to tissue-specific variations in TLR4 expression and the different dosages of hesperidin employed across studies.

Hesperidin, however, has a growing body of evidence demonstrating its ability to suppress reactive oxygen species (33) through various mechanisms, including inhibition of cyclooxygenase enzymes, which results in the suppression of inflammatory markers (34-36). In rats, hesperidin at doses of 100 mg/kg and 200 mg/kg has been shown to up-regulate the levels of the endogenous antioxidant enzyme glutathione in hepatocytes (37). Even a dose of 50 mg/kg of hesperidin has been reported to improve overall health status in a rat model (38). Collectively, these studies support our findings regarding the pro-inflammatory effect of atorvastatin and the anti-inflammatory effects of hesperidin.

According to the findings, it is observed that hesperidin has antioxidant protective effects against the hepatotoxic effects of atorvastatin when given in large doses. Therefore, monitoring of liver function is essential for patients who take atorvastatin as part of their prescribed medications, especially for those who are considered high-risk patients, such as those with pre-existing liver problems. Hesperidin was found to reduce liver damage in this situation.

Conflicts of Interest: The authors declare that there are no conflicts of interest that could have influenced this study.

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