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(RESEARCH ARTICLE)

Effect of Atorvastatin, Vitamin C, and Ginsenoside Rg1 on Improving Oxidative Stress and Interleukins in Hyperlipidemia in Male Rats

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Abstract

Background and Objective: Hyperlipidemia is a major risk factor in the development of oxidative stress and chronic inflammation within vascular and cellular tissues. Therefore, this physiological study aimed to evaluate the protective and therapeutic effects of atorvastatin, vitamin C, ginsenoside Rg1, atorvastatin + ginsenoside Rg1, and vitamin C + ginsenoside Rg1 in regulating oxidative stress biomarkers and inflammatory cytokines in the serum of male rats.

Experimental design: 35 male Sprague Dawley rats were used in the experiment, randomly divided into 7 groups of (5) rats each, including: a normal control group, a hyperlipidic group (fed on a high-fat diet with 2% cholesterol, beef fat and sugar), in addition to 5 hyperlipidic groups that were treated daily for 30 days as follows: atorvastatin (2 mg/kg), vitamin C (200 mg/kg), ginsenoside Rg1 (20 mg/kg), and the sixth and seventh groups were treated with (atorvastatin + Rg1) and (vitamin C + Rg1) respectively.

Results: The results showed that inducing hyperlipidemia led to a severe physiological deterioration characterized by a significant increase in the lipid peroxidation index (Isoprostane-8) and inflammatory cytokines (NF-κB, TNFα, IL-6), accompanied by a severe depletion of enzymatic and non-enzymatic antioxidants (GSH, CAT). In contrast, all therapeutic treatments reduced inflammation and peroxidation levels and enhanced the immune system ($P \leq 0.05$). The synergistic combination of Vitamin C and Ginsenoside Rg1 achieved the optimal physiological response, restoring these parameters to near-normal values.

Conclusion: We conclude from the current study that the physiological synergy between the natural antioxidant (vitamin C) and the bioactive compound (Rg1) has superior efficacy over monotherapy in suppressing the molecular mechanisms of oxidative stress and inflammation resulting from cellular lipid disorders.

Keywords: Hyperlipidemia; Atorvastatin; Vitamin C; Ginsenoside Rg1; Oxidative Stress; Cytokines; Interleukins.

1 Introduction

Hyperlipidemia (high lipid level in the blood) is one of the most important risk factors for cardiovascular disease, and it is strongly linked to oxidative stress. Key biomarkers of oxidative stress include isoprostane-8 (8-iso-PGF2α), reduced glutathione (GSH), and catalase (CAT). Several recent studies in animal models and cellular systems demonstrate that hyperlipidemia leads to increased levels of isoprostane-8, a sensitive marker of lipid oxidation, along with depletion of antioxidants such as reduced glutathione and catalase. These changes are associated with tissue damage, inflammation, and metabolic disturbances (Ma *et al*., 2022; Benson *et al*., 2023).

Hyperlipidemia, which is characterized by high levels of lipids in the blood such as total cholesterol, triglycerides, and low-density lipoprotein cholesterol, is a major risk factor for cardiovascular disease and metabolic disorders (Alwahsh *et al*., 2025). Current evidence indicates that hyperlipidaemia mainly induces chronic low grade inflammation by

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inducing important inflammatory pathways like the interleukin-6 (IL-6), nuclear factor kappa B (NF-κB), and tumour necrosis factor alpha (TNFα) (Zhang *et al*., 2023). These molecules play pivotal roles in regulating immune responses, promoting endothelial dysfunction, and accelerating atherosclerosis (Xu *et al*., 2024). Understanding the interplay between lipid metabolism and inflammatory signaling is crucial for developing effective strategies to prevent or treat hyperlipidemia-related complications.

High blood lipid levels play a significant part in oxidative stress and inflammation and are a significant risk factor for cardiovascular diseases. An imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses leads to oxidative stress, which causes lipid peroxidation, tissue damage, and endothelial dysfunction (Jin *et al*., 2024). Key biomarkers for assessing oxidative stress include isoprostanes (such as isoprostan-8), reduced glutathione (GSH), and catalase (CAT). Isoprostanes are reliable indicators of lipid peroxidation, while reduced glutathione and catalase are essential components of the cellular antioxidant defense system (Chen *et al*., 2024). The statin drug commonly used to treat hyperlipidaemia, atorvastatin, has a number of effects including anti-inflammatory and antioxidant (El Rabey et al., 2025). Based on these findings, it seems that the anti-inflammatory properties of atorvastatin in lipid disorders are mediated by its ability to inhibit NF-κB signaling, to downregulate innate immune pathways and to decrease expression of pro-inflammatory cytokines. Studies show that atorvastatin reduces NF-κB-associated gene expression and inhibits subsequent cytokine production, while cellular studies show dose-dependent decreases in TNFα and IL-6 expression in macrophages. Transcription inhibition by atorvastatin reduced NF-κB pathway activity in gene transcription analyses of dyslipidemia-affected mice and reduced TLR4 expression associated with innate immune activation (Inia *et al*., 2023; Yao *et al*., 2023).

Vitamin C is a major low molecular weight antioxidant that contributes to lipid protection from oxidation and supports enzymatic defense mechanisms such as glutathione and catalase. Recent studies have linked vitamin C levels to markers of oxidative stress, including F2-isoprostane, glutathione (GSH), and catalase (CAT), in cardiovascular and metabolic disorders associated with dyslipidemia. Lipid oxidation products, such as F2-isoprostane (8-isoprostane), are well-known biomarkers of oxidative lipid damage, and their levels are elevated in cardiovascular and metabolic diseases and other chronic disorders (Almulla *et al*., 2023; Nuñez-Selles *et al*., 2025).

In the field of hyperlipidemia, Rg1 and other ginsenosides have been shown to have lipid-lowering and antioxidant properties, through enhanced activity of antioxidant enzymes and inhibition of oxidative stress. Rg1 is considered one of the most promising adjunctive therapies for hyperlipidemia via antioxidant signaling pathways (Nrf2, AMPK, and others). Rg1 inhibits NF-κB signaling and reduces TNF-α and IL-6 levels in inflammatory models, and Rg1 ginsenosides also demonstrate lipid-lowering activity (Jin *et al*., 2023). Consequently, this study aimed to estimate the effect of Atorvastatin, Vitamin C (Ascorbic Acid), and Ginsenoside Rg1 in normalizing Isoprostane-8, GSH, and CAT levels with NF-κB, TNFα, and IL-6 levels resulting from hyperlipidemia in the serum of male rats.

2 Material and methods

2.1 Materials

Atorvastatin was obtained from Samarra Pharmaceuticals/Iraq, Vitamin C (Ascorbic Acid) formula $C_6H_8O_6$ from Macklin Pharmaceuticals/China, and Ginsenoside Rg1 from Sigma Pharmaceuticals/USA.

2.2 Animals

In this experiment, male Sprague Dawley rats that were four months old and weighed 200 ± 10 grams were employed. The rats were then housed in different cages under standard laboratory conditions, including 12:12 hours of light, and a temperature of 22 ± 2°C. The cages were also cleaned and disinfected. The animals were acclimatised to water and food for 2 weeks. During the experiment of 30 days, the healthy animals were fed their normal diet while the rest of the animals were fed a high-fat diet containing 2% cholesterol, 100 g of beef fat, and 100 g of sugar (Du et al., 2023).

2.3 Experimental Design

In this investigation 35 adult male albino rats of similar weights were used and grouped into seven groups of 5 rats. Groups 2-7 were made hyperlipidemic using the following methods:

- Control Group: Received a normal diet and distilled water for 30 days.
- (Hyperlipidaemic group): fed a high fat diet and given distilled water for 30 days.

- (Hyperlipidemia Group and Dosed with Atorvastatin): Given a high-fat diet and 2 mg/kg Atorvastatin for 30 days (Luo et al., 2024).
- 4.The Hyperlipidemia Group was fed a high fat diet for 30 days with Vitamin C (200 mg/kg) (Mohammed et al., 2023).
- In the fifth group, which received a high-fat diet and Ginsenosides at 20 mg/kg (Abdi et al., 2025) for 30 days, Ginsenoside Rg1 has been shown to be an effective treatment for hyperlipidaemia (Abdi et al., 2025).
- (Hyperlipidemia Group treated with Atorvastatin + Ginsenoside Rg1): For 30 days, this group received a high-fat diet along with 2.6 mg/kg of atorvastatin and 20 mg/kg of ginsenoside Rg1.
- (Hyperlipidemia Group treated with Vitamin C + Ginsenosides): High Fat Diet (HFD) was fed and vitamin C (30 mg/kg) and Ginsenoside Rg1 (20 mg/kg) were administered for 30 days.

2.4 Collection of Blood Serum

Thirty days after the trial was concluded, the animals were given intramuscular injections of 5 mg/kg of ketamine and 35 mg/kg of xylazine and food was withheld for 12 hours. The blood was taken from the heart and the blood serum was stored at -20°C for biochemical testing.

2.5 Biochemical and Histological Tests

The concentrations of Isoprostane-8, GSH and CAT in blood serum were evaluated according to the procedure of the kit developed by the French company Biolabo, based on the ELISA technique, and the concentration of NF-κB, TNFα and IL-6 were also measured.

2.6 Statistical Analysis

The statistical analysis results were conducted at a significance level of $P \geq 0.05$ using the Duncan multiple range test and SPSS software.

3 Results

3.1 Serum Isoprostane-8, GSH, and CAT Concentrations

The data in Figure 1 and Table 1 showed significant increase in the concentration of isoprostane-8 and significant decrease in the concentration of GSH and CAT, when compared to the normal control group. The concentration of GSH and CAT were seen to be higher in the vitamin C only group, ginsenoside Rg1 only group, atorvastatin + ginsenoside Rg1 group, and vitamin C + ginsenoside Rg1 group when compared to the hyperlipidemic group, while isoprostane-8 levels were the lowest in these groups. The group which was given both vitamin C and ginsenoside Rg1 treatment experienced the most improvement in the above-mentioned measures.

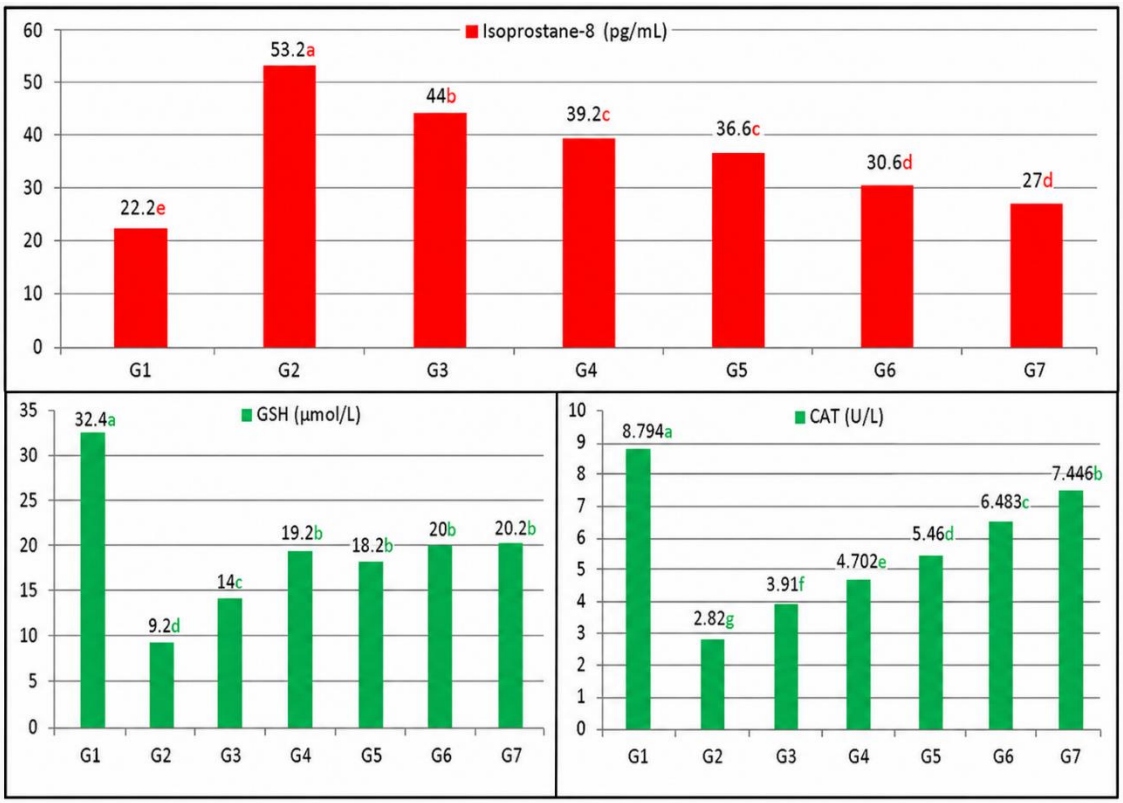

Figure 1 Concentrations of Isoprostane-8, GSH, and CAT in the serum of male rats

Table 1 The effect of Vitamin C and Ginsenoside Rg1 on the concentration of Isoprostane-8, GSH and CAT in serum of rats.

Parameters / Groups	Isoprostane-8 (pg/mL)	GSH (µmol/L)	CAT (U/L)
Control	22.20±3.42e	32.40±3.98a	8.794±0.385a
Hyperlipidemia	53.20±4.15a	9.20±1.92d	2.820±0.215g
Hyperlipidemia + Atorvastatin	44.00±3.162b	14.0±1.58c	3.910±0.360f
Hyperlipidemia + Vitamin C	39.20±3.96c	19.20±2.86b	4.702±0.336e
Hyperlipidemia + Ginsenoside Rg1	36.60±2.41c	18.20±1.92b	5.460±0.222d
Hyperlipidemia + Atorvastatin + Ginsenoside Rg1	30.60±2.41d	20.0±1.58b	6.483±0.224c
Hyperlipidemia + Vitamin C + Ginsenoside Rg1	27.00±2.24d	20.20±1.92b	7.446±0.180b
F	54.97	44.18	264.37
P-Value	<.0001***	<.0001***	<.0001***

The values represent mean ± the standard deviation.; Numbers followed by different letters for each line represent significant difference at 0.05 probability level.

3.2 Serum NF-κB, TNFα, and IL-6 Concentrations

In (Figure-2) and table (2), the hyperlipidaemic group had significantly higher (P≥0.05) concentration of NF-κB, TNFα and IL-6 than the normal control group. In the hyperlipidaemic group, the concentration of NF-κB, TNFα, and IL-6 was decreased but there was no significant change in the other groups (Atorvastatin only, Vitamin C only, Ginsenoside Rg1 only, (Atorvastatin + Vitamin C), and (Ginsenoside Rg1 + Vitamin C)). The combination of Vitamin C + Ginsenoside Rg1 was most effective in improving the above parameters.

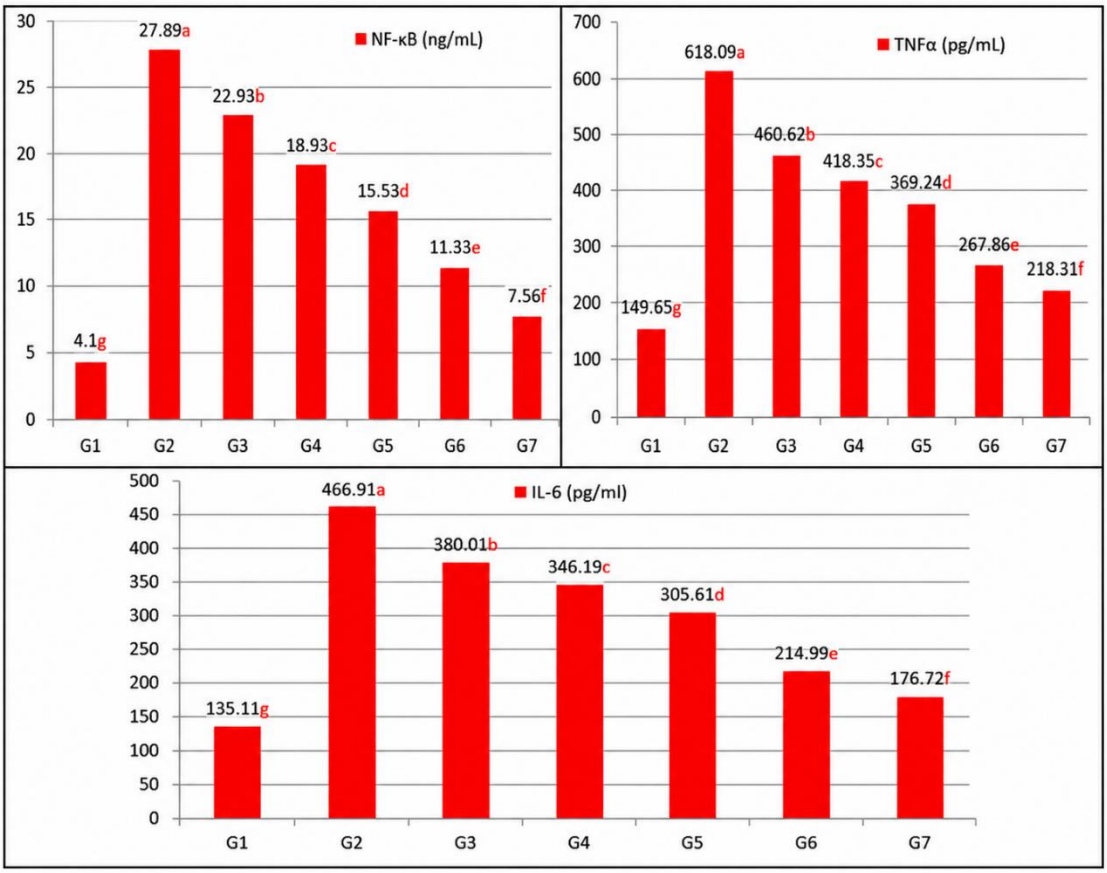

Figure 2 Effect of Vitamin C and Ginsenoside Rg1 on serum concentrations of NF-κB, TNFα, and IL-6.

Table 2 Effect of Vitamin C and Ginsenoside Rg1 on serum concentrations of NF-κB, TNFα, and IL-6 in serum male rats.

Parameters / Groups	NF-κB (ng/mL)	TNFα (pg/mL)	IL – 6 (pg/ml)
Control	4.10±0.30g	149.65±29.43g	135.11±8.24g
Hyperlipidemia	27.89±0.92a	618.09±21.61a	466.91±8.27a
Hyperlipidemia + Atorvastatin	22.93±0.72b	460.62±34.36b	380.01±20.15b
Hyperlipidemia + Vitamin C	18.93±0.72c	418.35±18.23c	346.19±22.60c
Hyperlipidemia + Ginsenoside Rg1	15.53±0.74d	369.24±24.55d	305.61±19.25d
Hyperlipidemia + Atorvastatin + Ginsenoside Rg1	11.33±1.02e	267.86±25.43e	214.99±12.13e
Hyperlipidemia + Vitamin C + Ginsenoside Rg1	7.56±1.19f	218.31±19.64f	176.72±12.30f
F	507.83	199.16	288.78
P-Value	<.0001***	<.0001***	<.0001***

The values represent mean ± the standard deviation. Numbers followed by different letters vertically indicate significant difference at a probability level of ($P \leq 0.05$).

4 Discussion

High lipid levels or hyperlipidemia lead to increased lipid peroxidation products (such as MDA) and 8-isoprostane, indicating oxidative damage to lipids in the brain and peripheral tissues of insulin-resistant rats fed a high-fat diet

(Edward *et al*., 2024). Hyperlipidemia results in decreased glutathione (GSH), the main intracellular antioxidant, particularly when glutathione peroxidase (GPx) activity is increased and glutathione is consumed during peroxide detoxification (Cristina *et al*., 2024). Experimental studies in animal models and clinical observations in humans consistently show that hyperlipidemia induces NF-κB signaling and increases the expression of pro-inflammatory cytokines such as TNFα and IL-6 in various tissues, including the liver, adipose tissue, vascular endothelium, and immune cells (Zhang *et al*., 2022). Interferences targeting these pathways, extending from dietary compounds to pharmacological agents, have also shown anti-inflammatory effects by inhibiting NF-κB activation and reducing TNFα/IL-6 production (He *et al*., 2023).

Studies confirm the beneficial role of atorvastatin in reducing oxidative stress associated with hyperlipidemia by lowering lipid peroxidation products (including isoprostanes), increasing glutathione levels, and enhancing catalase activity. Comparative studies indicate that dietary antioxidants, such as MDA, GSH, and CAT, can restore redox balance. While pharmacological interventions like atorvastatin are generally more effective, combination therapies may offer additional benefits (Khatiwada and Hong, 2024). These effects contribute to improved redox balance beyond cholesterol reduction alone, a key aspect of the multifaceted benefits of statins (El Rabey *et al*., 2025).

Atorvastatin reduces the mRNA levels of IL-6, TNFα, and cytokines in macrophages exposed to oxidized LDL protein in a concentration-dependent manner, supporting an endogenous anti-inflammatory effect (Liu *et al*., 2025). Multiple animal and cellular models of dyslipidemia and atherosclerosis have demonstrated a consistent decrease in NF-κB nuclear transcription factor activity and a reduction in TNFα and IL-6 levels following atorvastatin administration, with the degree of this decrease varying according to dose and context. These preclinical findings suggest mechanisms potentially relevant to hyperlipidemia and support the multiple anti-inflammatory effects of atorvastatin (Yao *et al*., 2023; Maranducă *et al*., 2025).

Vitamin C is described as a low molecular weight antioxidant that helps stop lipid peroxidation and may reduce cholesterol, low-density lipoprotein (LDL) oxidation, and vascular inflammation, all of which are factors related to hyperlipidemia (Jomova *et al*., 2023). Patients with coronary artery disease who also have hypertension and/or hyperlipidemia show significantly higher 8-isoprostane levels and lower blood vitamin C levels compared to healthy individuals, linking low vitamin C levels to increased oxidative lipid damage in dyslipidemia (El-Bawab *et al*., 2022). Glutathione (GSH) and catalase (CAT) are among the most important antioxidant defense mechanisms, both enzymatic and non-enzymatic, and are frequently used to assess oxidative stress balance (Nuñez-Selles *et al*., 2025). Vitamin C intake is associated with reduced levels of IL-6 and TNF-α in various tissues and cell types. Specifically, it decreases IL-6 and TNF-α levels in brain tissue and inhibits IL-6 release from contracting skeletal muscle. Vitamin C inhibits the production of interleukin-6, interleukin-12, and tumor necrosis factor-alpha (TNF-α), while increasing the production of interleukin-4 and interleukin-10 in mouse spleen cells. It also reduces the production of interleukin-2 and interleukin-6 in pig mononuclear cells. Furthermore, vitamin C reduces reactive oxygen species, decreases NF-κB activation, and can inhibit NF-κB binding to DNA and IκB phosphorylation (Gęgotek and Skrzydlewska, 2022).

Analysis of preclinical models of liver injury (of various etiologies) has shown that ginsenosides (including Rg1) significantly affect markers of oxidative stress such as glutathione (GSH), glutathione peroxidase (GSH-Px), and catalase (CAT), thereby improving overall antioxidant status. In liver injury caused by oxidative stress, Rg1 improves oxidative markers and lipid levels via Nrf2 and other pathways, supporting its role as an antioxidant and hepatoprotective agent (Bian *et al*., 2023). Fermented ginseng extracts (containing Rg1 and related ginsenosides and their transformation) increase the GSH/GSSG ratio and CAT activity in liver cells exposed to oxidative stress, indicating enhanced antioxidant defense (Park and Lee, 2026). Rg1 "inhibits the activation of NF-κB and MAPK signaling pathways," with a decrease in inflammatory cytokines; Rg1 reduces serum IL-6 and TNF-α levels and lowers p-p65/p-IκBα levels in a model of liver injury by LPS. Rg1 also reduces the phosphorylation of MyD88, NF-κB-p65, and IκBα, with a decrease in IL-6 and TNFα (Zhou *et al*., 2024). The comprehensive meta-analysis conducted on animals in diabetic patient models in 2023 also showed a positive effect on reducing levels of interleukin-6 and tumor necrosis factor-alpha, supporting an anti-inflammatory orientation (Xie *et al*., 2023).

5 Conclusion

The results of the current study demonstrate that induced hyperlipidemia leads to acute systemic physiological deterioration as a result of cellular redox imbalance and inflammatory stimulation. Elevated lipid levels strongly stimulate the molecular mechanisms of oxidative stress, as evidenced by a significant increase in the lipid peroxidation index Isoprostane-8, accompanied by a severe depletion of the antioxidant defense system (GSH and CAT). This disruption activates the inflammatory signaling pathway via NF-κB nuclear transcription, leading to increased production of pro-inflammatory cytokines (TNFα and IL-6).

Therapeutic procedures, on the contrary, have proved to be very effective in reducing this physiological imbalance. The anti-inflammatory and antioxidant properties of atorvastatin, inhibition of reactive oxygen species (ROS) oxidation by vitamin C, and enhancement of defense enzymes through crucial cellular pathways by ginsenoside Rg1 are additional factors that contribute to the beneficial effects of the drug. The combination of vitamin C and ginsenoside Rg1 is considered the physiological strategy for restoring vital indicators to their normal levels.

Compliance with ethical standards

Statement of ethical approval

The study was carried out in compliance with the ethical standards for animal experimentation and all the ethical and official approvals were obtained from the local animal care and use committee.

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