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COMBINED VITAMIN C AND GINSENOSE Rg1 ATTENUATE HYPERLIPIDEMIA-INDUCED DNA DAMAGE AND INFLAMMATORY RESPONSES VIA MODULATION OF STAT3 AND MIP2 SIGNALING PATHWAYS

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ABSTRACT

Background: Hyperlipidemia is a major factor in metabolic disorders, as it physiologically induces oxidative stress and DNA damage, as well as modulating immune responses towards inflammation by activating pathogenic cellular pathways such as STAT3 protein and Mip2 chemokine. Hence, the purpose of this study was to investigate the individual and combined anti-oxidative and anti-inflammatory effects of atorvastatin, vitamin C and ginsenoside Rg1. **Experimental design:** The animals used in this study were 35 male Sprague Dawley rats, which were randomly allocated to 7 groups of 5 rats each and fed a normal control diet, hyperlipidic diet (high-fat diet), hyperlipidic diet + atorvastatin (2 mg/kg), hyperlipidic diet + vitamin C (200 mg/kg), hyperlipidic diet + Ginsenoside Rg1 (20 mg/kg), hyperlipidic diet + combination (atorvastatin + Ginsenoside Rg1), hyperlipidic diet + combination (vitamin C + Ginsenoside Rg1) for 30 days. **Results:** The hyperlipidemia group showed a significant increase in markers of oxidative stress and cellular damage (MDA and 8-OHdG) and inflammation (STAT3 and Mip2), contrasted with a sharp decrease in antioxidants (SOD and GPx) and the anti-inflammatory cytokine (IL-10) compared to the normal control ($P \leq 0.05$). All treatments significantly reversed the pathological changes. The combination of vitamin C with ginsenoside Rg1 had the most favourable physiological effects, with a significant decrease in MDA and 8-OHdG, a recovery of SOD and GPx activity, and a clear increase in IL-10 concentration, compared with hyperlipidaemic group. **Conclusion:** It is concluded that hyperlipidemia induces a profound physiological imbalance, and that combining vitamin C with Ginsenoside Rg1 provides superior synergistic protection that surpasses single treatments in suppressing oxidative stress and cellular inflammation.

Keywords: Hyperlipidemia, Atorvastatin, Vitamin C, Ginsenoside Rg1, 8-OHdG, STAT3, Signaling Pathways.

1 INTRODUCTION

High blood lipid levels are a major risk factor for metabolic disorders. A growing body of research suggests that high blood lipid levels promote oxidative stress, leading to increased lipid peroxidation and DNA damage, while simultaneously weakening antioxidant defense systems. Malondialdehyde (MDA) as a lipid peroxidation biomarker, “8-hydroxy-2'-deoxyguanosine (8-OHdG) as an oxidative DNA damage biomarker, and antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) are key biomarkers used to assess these processes. Studies conducted on animal and human models consistently show that elevated blood lipid levels raise MDA and 8-OHdG levels, while reducing SOD and GPx activity, reflecting increased oxidative stress and impaired antioxidant capacity (Nie *et al.*, 2024; Magaña-Rodríguez *et al.*, 2024; Khursheed *et al.*, 2026). Hyperlipidemia also shifts immune signaling toward inflammation. The presence of high body fat percentages is linked to an increase in the level of the protein interleukin-6 (IL-6) and with activation of the protein STAT3”. Anti-inflammatory signaling of the protein interleukin-10 (IL-10) is on the other hand often weak or even missing. The strongest evidence comes from models of inflammation associated with metabolic liver disease, cardiovascular disease, and obesity, where hyperlipidemia (high levels of LDL cholesterol, oxidized LDL cholesterol, fatty acids, or a high-fat diet) leads to increased inflammatory signaling and tissue damage (Yang *et al.*, 2024; Jiang *et al.*, 2024).

IL-10 is a central anti-inflammatory cytokine, and its known end effector is STAT3. However, while IL-6-STAT3 typically stimulates inflammatory or tissue-damaging programs, IL-10-STAT3 contributes to inflammation resolution and immune suppression (Samad *et al.*, 2025). High blood lipids are associated with metabolic inflammation, and hyperlipidemia can lead to macrophage activation and increased secretion of inflammatory chemokines in metabolic diseases. Mice fed a high-fat diet showed dyslipidemia and an inflammatory pattern in macrophages. Saturated fatty acids also induced the production of Cxcl2, as well as Tnf, Il6, and Cxcl10 in macrophages. MIP-2/CXCL2 is part of a broader lipid-stimulated chemokine response, and inflammation induced by hyperlipidemia involves macrophage activation and chemokine-mediated leukocyte recruitment (Ullah *et al.*, 2023; Panico *et al.*, 2024). The evidence presented supports decreases in malondialdehyde (MDA) and increases in SOD and GPx/GSH-Px with atorvastatin (Yan *et al.*, 2024; Chen *et al.*, 2025). Atorvastatin is a key lipid-lowering drug for treating lipid disorders. It also possesses multifaceted anti-inflammatory effects through HMG-CoA reductase inhibition and subsequent modulation of immune signaling. In models associated with hyperlipidemia, the most compelling evidence points to cytokine rebalancing, with elevated interleukin-10 levels in some cases, and broader suppression of inflammatory mediators such as interleukin-1 β , interleukin-6, TLR/NF- κ B receptors, and NLRP3 (Cheng *et al.*, 2022).

Vitamin C acts as a water-soluble antioxidant and electron donor that neutralizes reactive oxygen species, and it can improve nitric oxide bioavailability and redox balance in the vascular endothelium. Metabolic studies indicate that low vitamin C levels are associated with metabolic syndrome and lipid metabolism disorders, supporting its biological importance in dyslipidemia. Vitamin C reduces MDA and 8-OHdG levels while restoring SOD and GPx levels (Panda *et al.*, 2022; Wróblewska *et al.*, 2025). In hyperlipidemia models, vitamin C consistently uplifts anti-inflammatory IL-10 signaling indirectly or context-dependently and reduces inflammatory STAT3 activation (Nusair *et al.*, 2026).

Rg1 was given for four weeks to rats given a high-fat diet and treated with streptozotocin. This improved both oxidative stress and lipid levels, indicating the possibility of concurrent antioxidant and lipid-related effects in metabolic illnesses (Peng *et al.*, 2022). Rg1 suppresses NF- κ B and lowers inflammatory factors and fat buildup in the liver in biliary liver damage caused by alpha-naphthylisothiocyanate (ANIT) (Shang *et al.*, 2025). Additionally, STZ-induced type 1 diabetic mice's pancreas and spleen produced less IL-1 β , TNF- α , NOS2, CXCL16, NF- κ B, and TF when Rg1 was present (Zong *et al.*, 2023). The aim of this study was to determine how atorvastatin, vitamin C (ascorbic acid), and ginsenoside Rg1 affected the serum levels of MDA, 8-OHdG, SOD, and GPx in male rats that were normalised by hyperlipidemic serum levels of IL10, STAT3, and Mip2.

2 MATERIALS AND METHODS

2.1 Materials

The source of atorvastatin was “Samarra Pharmaceuticals (Samarra, Iraq). Vitamin C (Ascorbic acid, C₆H₈O₆; purity $\geq$ 98%) and Ginsenoside Rg1 (C₄₂H₇₂O₁₁)” were purchased from Macklin Inc., (Shanghai, China) and Sigma-Aldrich (St. Louis, MO, USA), respectively.

2.2 Animals

In this investigation, forty adult male Sprague-Dawley rats weighing 200 $\pm$ 10 g and four months old were employed. The animals were housed in polypropylene cages with a regulated temperature of 22 $\pm$ 2 °C, a 12-hour light/dark cycle, and conventional sanitation and hygiene practices. Before the experimental procedures began, rats were given regular food and unlimited access to tap water while they were acclimated to laboratory surroundings for two weeks. For the

duration of the 30-day experiment, the control group was fed a typical commercial meal. According to Du et al. (2023), the experimental groups were fed a high-fat diet (HFD) that included regular chow enriched with 2% cholesterol, 100 g of beef tallow, and 100 g of sucrose.

2.3 Experimental Design

Thirty-five adult male "Sprague-Dawley rats, with a similar body weight distribution, were randomly divided into seven groups of five rats each. Each member of group 1 was given distilled water orally and was fed a standard diet and was treated as a normal control. Animals in the other six groups (Groups 2, 3, 4, 5, 6 and 7) remained on a high-fat diet (HFD) for 30 days. The respective diets and daily oral treatments were administered as follows: Group 2 was given only distilled water as their drinking water, while Group 3 was treated with Atorvastatin (2 mg/kg/day), Group 4 was treated with Vitamin C (200 mg/kg/day), Group 5 was treated with Ginsenoside Rg1 (20 mg/kg/day), Group 6 was treated with Atorvastatin (2 mg/kg/day) and Ginsenoside Rg1 (20 mg/kg/day), and Group 7 was treated with Vitamin C (200 mg/kg/day) and Ginsenoside Rg1" (20 mg/kg/day) during this 30-day period.

2.4 Blood Collection and Serum Preparation

All rats were given free drinking water and denied food for "12 hours following the 30-day trial period. After that, an intramuscular (i.m.) injection of a combination of ketamine (90 mg/kg) and xylazine (10 mg/kg) was used to sedate the animals. Without the use of an anticoagulant, blood samples were taken straight into simple tubes. To extract the serum, the samples were centrifuged for 15 minutes at 4 °C at 3,000×g after being allowed to clot for 30 minutes at room temperature". For biochemical and immunological investigations, the separated serum was promptly fractionated and kept at -20 °C.

2.5 Biochemical and Immunological Assays

Malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG), two oxidative stress markers, were evaluated in serum using enzyme linked immunosorbent assay "(ELISA) kits (Biolabo, France) in accordance with the manufacturer's instructions. Furthermore, the anti-inflammatory cytokine interleukin-10 (IL-10) and inflammatory signaling mediators STAT3 and macrophage inflammatory protein-2 (MIP-2/CXCL2) were measured in serum by using specific rat ELISA kits (Biolabo France)" according to the manufacturer's instructions. The absorbances were determined at the specified wavelengths, using a microplate spectrophotometer.

2.6 Statistical Analysis

All data were presented as mean $\pm$ standard deviation (SD). "IBM SPSS Statistics software (Version 26.0; IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The difference between the experimental groups was evaluated by one-way Analysis of Variance (ANOVA) and then Duncan's Multiple Range Test for multiple comparisons was used". Differences were deemed to be significant at $P < 0.05$.

3 RESULTS

3.1 Serum MDA, 8-OHdG, SOD, and GPx Concentrations

The serum malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels were significantly elevated in hyperlipidemic rats (Group 2) while the activities of SOD and glutathione peroxidase (GPx) were significantly reduced when compared with the levels in the normal control rats (Group 1), as shown in Figure 1 and Table 1. Monotherapy using "Atorvastatin (Group 3), Vitamin C (Group 4) and Ginsenoside Rg1 (Group 5) were found to substantially inhibit levels of serum MDA and 8-OHdG, and to significantly increase the serum enzymatic activity of SOD and GPx from hyperlipidemic groups ($P < 0.05$). Co-treatment regimens were even more effective in improving antioxidant status and reducing oxidative damage. Importantly, the combination of Vitamin C and Ginsenoside Rg1 (Group 7) showed the highest therapeutic effects on decreasing MDA and 8-OHdG levels and improving the activity of SOD and GPx, compared with all other groups (Groups 1–6) and the Atorvastatin + Ginsenoside Rg1 combination (Group 6)" ($P < 0.05$).

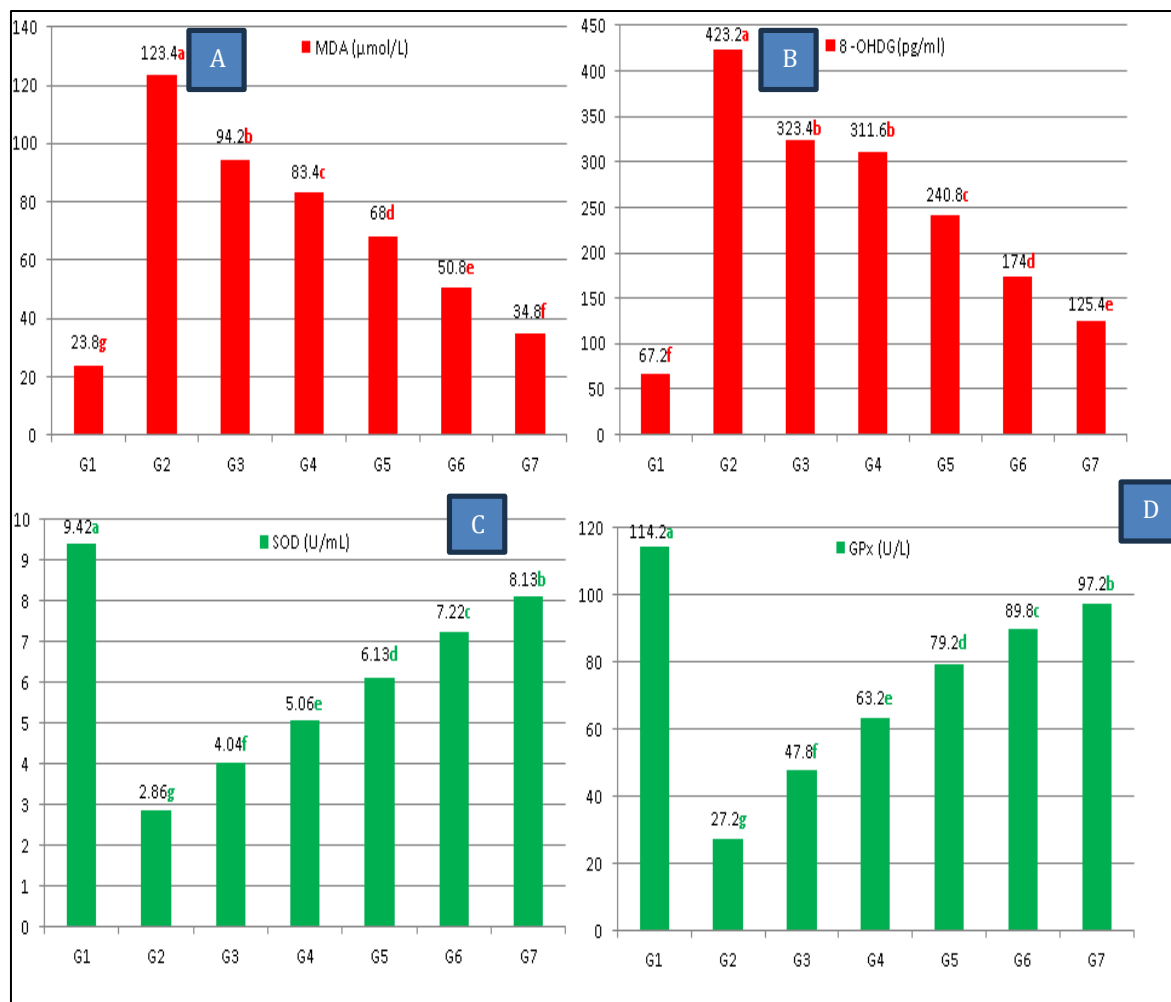


Figure 1: Atorvastatin, Vitamin C, Ginsenoside Rg1 and their combination effects on oxidative stress and antioxidant status in hyperlipidemic rats serum biomarker.

(A) Level of malondialdehyde ($\mu\text{mol/L}$). The concentration of 8-hydroxy-2'-deoxyguanosine (pg/mL) (B). (C) Superoxide dismutase (SOD) activity (U/mL) Glutathione peroxidase (GPx) activity (U/L) (D) All data have been expressed as mean $\pm$ SD (n=5). "Differences indicated by letters (a–g) are statistically significant ($P < 0.05$) according to One-way ANOVA and Duncan's multiple range test".

Table 1: Comparative effects of Atorvastatin, Vitamin C, Ginsenoside Rg1, and their combinations on serum oxidative stress markers (MDA and 8-OHdG) and antioxidant enzyme activities (SOD and GPx) in hyperlipidemic rats.

Parameters	MDA ($\mu\text{mol/L}$)	8-OHdG(pg/ml)	SOD (U/mL)	GPx (U/L)
Control	23.80 $\pm$ 3.65g	67.20 $\pm$ 12.46f	9.42 $\pm$ 0.29a	114.20 $\pm$ 8.47a
Hyperlipidemia	123.40 $\pm$ 6.78a	423.20 $\pm$ 16.42a	2.86 $\pm$ 0.20g	27.20 $\pm$ 3.65g
Hyperlipidemia + Atorvastatin	94.20 $\pm$ 3.19b	323.40 $\pm$ 17.11b	4.04 $\pm$ 0.20f	47.80 $\pm$ 5.40f
Hyperlipidemia + Vitamin C	83.40 $\pm$ 4.47c	311.60 $\pm$ 16.79b	5.06 $\pm$ 0.32e	63.20 $\pm$ 3.58e
Hyperlipidemia + Ginsenoside Rg1	68.00 $\pm$ 6.19d	240.80 $\pm$ 14.97c	6.13 $\pm$ 0.38d	79.20 $\pm$ 3.85d
Hyperlipidemia + Atorvastatin + Ginsenoside Rg1	50.80 $\pm$ 3.85e	174.00 $\pm$ 15.23d	7.22 $\pm$ 0.21c	89.80 $\pm$ 3.49c
Hyperlipidemia + Vitamin C + Ginsenoside Rg1	34.80 $\pm$ 3.65f	125.40 $\pm$ 16.71e	8.13 $\pm$ 0.23b	97.20 $\pm$ 3.65b
F	274.78	312.56	369.23	189.02
P-Value	<.0001***	<.0001***	<.0001***	<.0001***

• "The arithmetic mean $\pm$ standard deviation is represented by the values"; • "A statistically significant difference at a probability level of ($P \geq 0.05$) is indicated by numbers followed by distinct letters vertically".

3.2 Serum IL10, STAT3, and Mip2 Concentrations

In contrast to the normal control group (Group 1), the induction of hyperlipidemia (Group 2) resulted in a significant inflammatory response, as shown by a statistically significant increase in serum STAT3 and macrophage inflammatory protein-2 (MIP-2/CXCL2) levels, as well as a marked downregulation of the anti-inflammatory cytokine interleukin-10 (IL-10) ($P < 0.05$). Serum STAT3 and MIP-2 concentrations were significantly reduced by monotherapies with atorvastatin (Group 3), vitamin C (Group 4), or ginsenoside Rg1 (Group 5). At the same time, IL-10 levels were restored in comparison to the untreated hyperlipidemic group ($P < 0.05$). The immunomodulatory effects of dual combination therapy were better than those of solo treatments. Significantly outperforming all other treated groups, including the Atorvastatin + Ginsenoside Rg1 combination (Group 6), co-administration of Vitamin C and Ginsenoside Rg1 (Group 7) produced the most profound anti-inflammatory efficacy, achieving the highest elevation in IL-10 levels and the most substantial reduction in STAT3 and MIP-2 expression ($P < 0.05$).

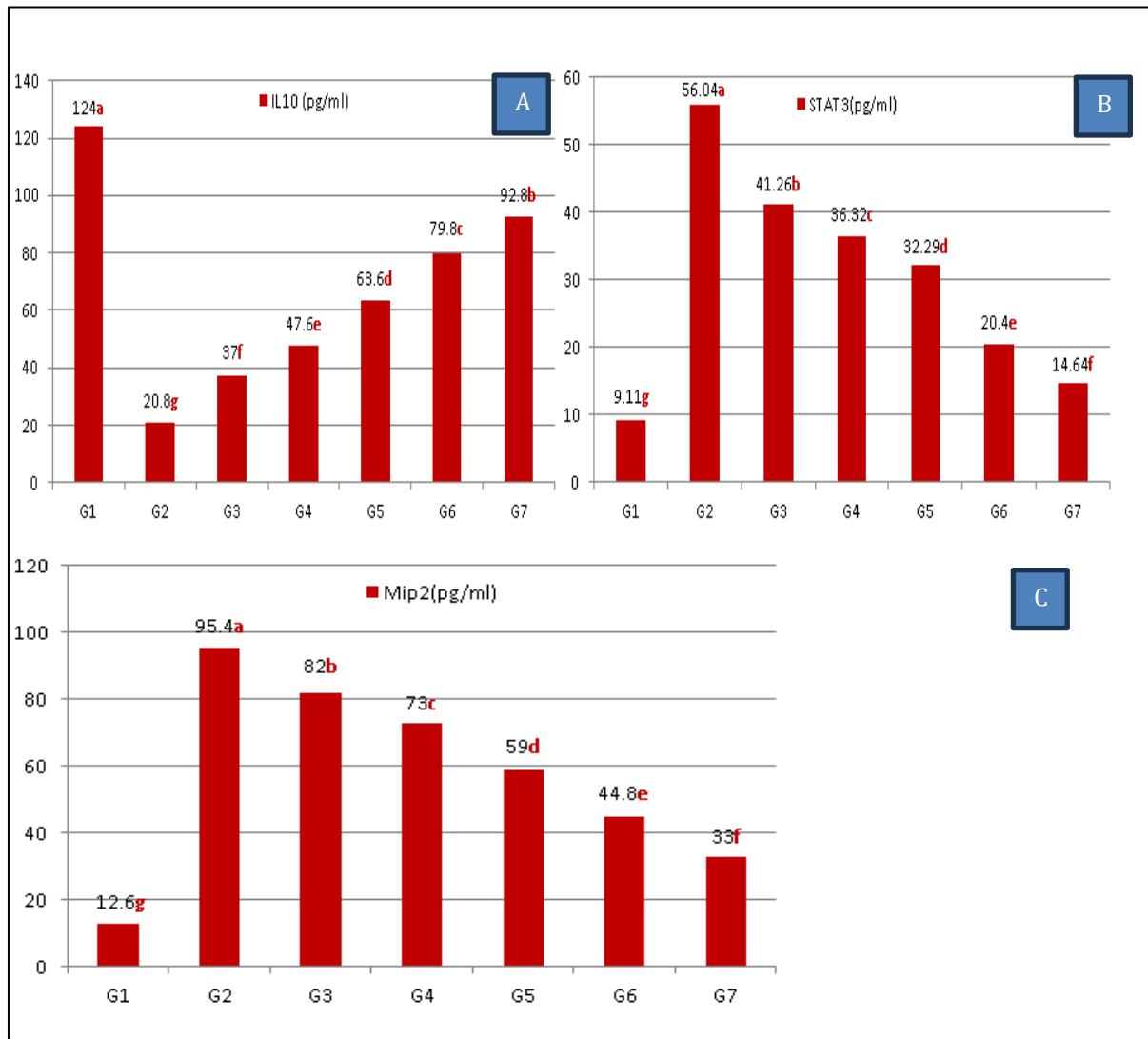


Figure 2: Immunomodulatory effects on serum inflammatory markers in hyperlipidemic rats of atorvastatin, vitamin C, ginsenoside Rg1, and their combination regimens. (A) The concentration of interleukin-10 (IL-10) (pg/mL). (B) The concentration of STAT3 (signal transducer and activator of transcription 3) (pg/mL). (C) Concentration of macrophage inflammatory protein-2 (MIP-2/CXCL2) (pg/mL). The data are presented as mean $\pm$ SD ($n=5$). Statistically significant differences at $P < 0.05$ are shown by bars with various superscript letters (a–g) (one-way ANOVA followed by Duncan's multiple range test).

Table 2: How atorvastatin, vitamin C, ginsenoside Rg1, and their combination regimens affect serum anti-inflammatory cytokines (IL-10) and inflammatory signaling mediators (STAT3 and MIP-2) in hyperlipidemic rats.

Groups	Parameters	IL10(pg/ml)	STAT3(pg/ml)	Mip2(pg/ml)
Control		124.00±9.51a	9.11±0.82g	12.60±2.07g
Hyperlipidemia		20.80±3.03g	56.04±3.22a	95.40±3.21a
Hyperlipidemia + Atorvastatin		37.00±3.54f	41.26±1.52b	82.00±2.24b
Hyperlipidemia + Vitamin C		47.60±4.45e	36.32±2.37c	73.00±3.16c
Hyperlipidemia + Ginsenoside Rg1		63.60±4.78d	32.29±1.74d	59.00±3.16d
Hyperlipidemia + Atorvastatin + Ginsenoside Rg1		79.80±5.17c	20.40±2.36e	44.80±2.86e
Hyperlipidemia + Vitamin C + Ginsenoside Rg1		92.80±3.19b	14.64±1.61f	33.00±3.16f
F		228.20	228.20	510.23
P-Value		<.0001***	<.0001***	<.0001***

• “The arithmetic mean ± standard deviation is represented by the values”; • “A statistically significant difference at a probability level of ($P \geq 0.05$) is indicated by numbers followed by distinct letters vertically”.

4 DISCUSSION

The evidence strongly confirms that hyperlipidemia induces oxidative stress, as evidenced by increased MDA (a product of lipid peroxidation) and elevated 8-OHdG (an indicator of DNA oxidation), along with decreased activity of the antioxidant enzymes SOD and GPx in multiple tissues (Duan and Li, 2023; Magaña-Rodríguez *et al.*, 2025). This defect contributes to cellular dysfunctions involved in the “development of cardiovascular diseases, neurodegeneration, reproductive impairment, the development of fatty liver/non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, kidney injury, pancreatic dysfunction, and even the risk of cancer through genomic instability resulting from persistent oxidative DNA damage” (Zang *et al.*, 2024; Magaña-Rodríguez *et al.*, 2025). Hyperlipidemia alters both the quantity and function of IL-10/STAT3 signaling, with the biological effect depending on which signal is dominant in the initial stages. When IL-6, ox-LDL, saturated fatty acids, or a high-fat diet stimulate STAT3, the outcome tends to be inflammatory, lipotoxic, or fibrotic (Zhu *et al.*, 2023; He *et al.*, 2024).

Activation of Ox-LDL and IL-6 leads to VAV3 inhibition and exacerbation of glucose and lipid processing in hepatocytes, which is consistent with the pathogenic hepatic STAT3 program in metabolic fatty liver disease (Jiang *et al.*, 2024). The data suggest, mechanistically, that hyperlipidemia increases MIP-2/CXCL2 via increased lipids, particularly saturated fatty acids, which stimulate inflammatory activation in macrophages under metabolic stress. The same model links this response to endoplasmic reticulum stress and NF-κB-associated inflammatory signaling, indicating that MIP-2 reflects a broader maladaptive macrophage program rather than the effect of a single pathway (Panico *et al.*, 2024).

Atorvastatin reduces MDA levels in hyperlipidemia and fatty liver mice fed a high-fat, high-sugar diet, compared to control mice. It also increases SOD and GPx levels in both serum and liver tissue, indicating improved antioxidant capacity in various tissues (Wang *et al.*, 2025). Atorvastatin alters cytokine responses towards a Th2/IL-10 pattern and M2 macrophage polarization via mevalonate and ROCK-related pathways. Studies indicate that high doses of atorvastatin reduce STAT3 in addition to IL-6 and NLRP3 signaling, which implies inhibition of primary inflammatory transcriptional programs (Khan *et al.*, 2025).

Vitamin C has been repeatedly described as an antioxidant strategy in diabetes, cardiovascular and metabolic diseases, and oxidative vascular stress. Experimental studies have shown a decrease in MDA levels and a stronger antioxidant status following vitamin C exposure. Evidence also consistently points to decreased SOD and GPx/GSH-Px levels in hyperlipidemia or high lipid levels, and increased levels when oxidative damage is mitigated. In contrast, 8-OHdG is a well-established marker of DNA oxidation, but current studies do not provide sufficient direct evidence that vitamin C specifically reduces 8-OHdG levels in hyperlipidemia (Yang, 2025; Luo *et al.*, 2025). In guinea pigs fed a diet rich in palm oil, and in palmitate-treated liver cells, ascorbate reduced the level of SOCS3 in the liver and reduced STAT3 phosphorylation. Researchers have explicitly linked SOCS3 inhibition to a decrease in STAT3 levels (Wang *et al.*, 2022).

Rg1 directly supports reduced MDA levels in conjunction with a broader improvement in antioxidants. It indirectly supports improved 8-OHdG-like DNA/RNA oxidative damage, and 8-OHG levels are a closely related indicator of oxidative nucleic acid damage. Elevated SOD and GPx levels are also directly supported (Yang *et al.*, 2022). Rg1 tends to

improve dyslipidemia and suppress inflammatory pathways. Rg1 alters immune homeostasis, inhibits inflammatory mediators, improves gut microbiota-associated metabolic inflammation, and activates pathways such as PI3K/Akt, SIRT1/Nrf2, and AHR/IL-22 (Wang *et al.*, 2025; Zhang *et al.*, 2025).

5 CONCLUSIONS

This study concludes that hyperlipidemia induces oxidative stress by elevating MDA and 8-OHdG levels, while inhibiting antioxidant enzyme defenses such as SOD and GPx. It also shifts the immune response towards an inflammatory pattern by increasing the expression of inflammatory markers STAT3 and Mip2 and suppressing the anti-inflammatory cytokine IL10.

The use of atorvastatin, vitamin C, and ginsenoside Rg1 (individually) demonstrated remarkable efficacy in reducing oxidative and inflammatory markers and restoring vital enzymes. However, the combination therapy, specifically the dual “combination of vitamin C and ginsenoside Rg1, achieved the best physiological synergy; it exhibited the greatest and most pronounced efficacy in suppressing oxidative stress (by reducing MDA and 8-OHdG and increasing SOD and GPx) and alleviating systemic cellular inflammation (by reducing STAT3 and Mip2 and increasing IL10)” compared to the individual treatments.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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