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The Therapeutic Effect of Olive Oil and Sheep Tallow on Liver Alterations Linked to Induced Atherosclerosis in Male Albino Rats

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Abstract

Background: Atherosclerosis is a chronic, multifactorial disease characterized by the accumulation of lipid-rich plaques within the arterial endothelium, frequently resulting in multi-organ morbidity. Given the central role of the liver as the primary metabolic hub for lipid homeostasis, this study investigated the therapeutic potential of olive oil (OO) and sheep tallow (ST) in mitigating atherosclerosis-associated hepatic structural and functional alterations.

Methodology: Atherosclerosis was experimentally induced in rats using an atherogenic diet (AGD). The subjects were randomized into six equal groups (n = 7 rats/group): normal baseline control, atherogenic positive control, untreated atherogenic negative control, and three experimental groups treated with simvastatin, ST, or OO. This study evaluated the serum lipid profiles, hepatic protein concentrations, and liver enzyme activities, along with comprehensive histopathological examinations of the hepatic tissues.

Results: AGD administration induced marked dyslipidemia and hepatic dysfunction. However, therapeutic interventions with OO and ST substantially ameliorated the disrupted serum lipid profiles. Furthermore, serum total protein and globulin levels exhibited highly significant improvements ($p < 0.0001$) following OO and ST administration. The elevated hepatic enzyme activities characteristic of atherogenic injury were significantly attenuated by both dietary fats, most notably by alanine aminotransferase (ALT; $p < 0.0001$). Histomorphological evaluations confirmed that OO and ST treatments promoted significant hepatocellular repair, considerably reducing necrosis, vacuolation, degeneration, and inflammatory infiltration, which were mainly observed in the untreated atherogenic group.

Conclusion: OO and ST administration in experimental rats exerted therapeutic and hepatoprotective effects, effectively restoring lipid homeostasis and ameliorating functional and structural hepatic alterations induced by atherosclerosis.

Article Info

Keywords:
Atherosclerosis, Dyslipidemia, Hepatoprotective, Histopathology, Liver protein, Alanine aminotransferase (ALT), Olive oil, Sheep tallow, Wistar albino rats.

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1. INTRODUCTION

Cardiovascular disease (CVD) encompasses a spectrum of pathological conditions that affect the heart and vasculature [1]. Among these, atherosclerosis is the predominant and life-threatening etiology [2]. As a leading global health burden, atherosclerotic cardiovascular disease was responsible for approximately 13 million deaths worldwide in 2022 [3]. Atherosclerosis is a chronic, complex, and progressive inflammatory disease [4, 5]. It frequently remains clinically insidious and asymptomatic for prolonged periods, propagating across multiple vascular beds before manifesting as critical ischemic events, including stroke, myocardial infarction, and peripheral artery disease [6]. The multifactorial nature of atherosclerosis involves a complex interplay of genetic and modifiable lifestyle risk factors, such as smoking, dietary habits, and physical inactivity, which

collectively exacerbate disease progression [7]. The histological hallmark of atherosclerosis is an atheroma, a lipid-rich plaque that develops within the arterial intimal layer, progressively compromising vascular patency and endothelial integrity [8]. Hyperlipidemia, particularly hypercholesterolemia, is a well-established primary risk factor for atherosclerosis. This dyslipidemic state is clinically characterized by elevated serum concentrations of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), concomitant with reduced high-density lipoprotein cholesterol (HDL-C [9]. Furthermore, impaired systemic lipid metabolism, specifically the aberrant processing and clearance of cholesterol and its esters, drives subendothelial accumulation of atherogenic lipoproteins, thereby initiating and sustaining the atherosclerotic cascade [10]. Beyond localized vascular manifestations, atherosclerosis is intrinsically linked to the pathogenesis of systemic multi-organ morbidities driven by dyslipidemia, chronic inflammation, and oxidative stress [11]. Notably, atherosclerotic progression significantly elevates the risk of profound cerebrovascular and neurodegenerative complications, including ischemic stroke and Alzheimer's disease (AD) [12]. Furthermore, contemporary vascular paradigms suggest that atherosclerotic-like calcification processes may also contribute to the pathogenesis of calcium oxalate nephrolithiasis [13]. The liver serves as the primary metabolic hub of the body, intricately regulating systemic homeostasis, energy metabolism, detoxification, and immunological responses [14, 15]. Crucially, it orchestrates lipid and cholesterol metabolism and acts as the principal site for lipoprotein synthesis, uptake, and secretion into the systemic circulation [16]. Disruptions in hepatic lipid homeostasis can precipitate chronic liver disease, which in turn exacerbates systemic dyslipidemia. This bidirectional relationship establishes a detrimental feedback loop in which hepatic dysfunction accelerates atherogenesis, whereas systemic dysmetabolism further deteriorates liver architecture and function [16, 17]. Dietary lipids critically influence cellular structural integrity and complex metabolic and endocrine pathways, serving as the primary energy reservoir in biological systems [18]. Extensive evidence demonstrates that the quantity, biochemical composition, and origin of dietary lipids fundamentally dictate the serum lipid profile [19]. Animal-derived adipose tissues [20], such as sheep and bovine tallow, primarily consist of triglycerides and specific essential fatty acids [21, 22]. Conversely, plant-derived sources, such as olive oil (extracted from *Olea europaea* fruit), provide a dense concentration of monounsaturated fatty acids (MUFAs), primarily oleic acid, along with potent bioactive minor constituents [23]. The consumption of olive oil is strongly correlated with pleiotropic health benefits, including enhanced cardiometabolic profiles, attenuation of oxidative stress, and anti-inflammatory properties [24]. Given the established mechanistic link between atherosclerosis and structural or functional hepatic alterations, targeted nutritional interventions are promising for improving health. Therefore, this study in experimental rats aimed to investigate the therapeutic efficacy of olive oil and sheep tallow in mitigating atherosclerosis-induced hepatic dysfunction and evaluate their potential to restore and maintain overall physiological systemic homeostasis.

2. MATERIALS AND METHODS

2.1. Tallow Preparation

Sheep fat samples were excised during the slaughter and butchering of local sheep aged a minimum of 12 months old. Samples were procured from an official butchery in Dhamar City, Yemen, specifically targeting adipose tissue surrounding the kidneys, tripe, heart, mesentery, and sheep tail. The detailed protocols for tallow extraction and route of administration have been previously described [25].

2.2. Olive Oil

Virgin olive oil in liquid form (Almanar Co., Syria) was procured from a commercial supplier in Dhamar City, Yemen.

2.3. Simvastatin Formulation

Simvastatin was obtained from a commercial pharmacy in Dhamar, Yemen. The established dose for the rat model is 0.18 mg/day per 200 g of body weight, dissolved in 100 mL distilled water (DW) [26]. A daily suspension was prepared by pulverizing the tablets and dissolving the resulting powder in DW.

2.4. Experimental Animals

This study utilized 49 healthy adult male Wistar albino rats (*Rattus rattus*), aged three months and weighing between 160 and 200 g, procured from the Animal House at the Faculty of Science, Sana'a University. The animals were housed in clean, appropriately sized stainless steel cages within a climate-controlled facility (22±2℃, 60% ventilation) under a standard 12-hour light/dark cycle. The rats were acclimated to these conditions for two weeks before the onset of the experiment. All subjects were provided *ad libitum* access to water and a standard chow diet containing all requisite macro- and micronutrients [27]. Animal care and experimental protocols complied strictly with the "Ethical Considerations in Animal Studies" guidelines [28] and were approved by the Committee of Experimental Animals Care and Use at the Faculty of Science, Sana'a University, Yemen (ethical code: BAHSS 101).

2.5. Experimental Design and Groups Division

The study spanned an investigative period of six months, which was divided into two distinct three-month stages. Stage 1 focused on the induction of atherosclerosis using an atherogenic diet (AGD), specifically a CCT formulation comprising 4% cholesterol, 1% cholic acid, and 0.5% thiouracil (w/w) [29]. Stage 2 evaluated the therapeutic interventions administered daily to the respective groups. Following a two-week acclimation period, the 49 rats were randomly assigned to six groups (n = 7 per group):

· **Group I (N):** Normal control group serving as a baseline reference. One milliliter of DW was administered orally throughout both stages.

· **Group II (Ath):** Positive control for atherosclerosis induction. Received 1 ml/kg body weight (b.w.) of AGD concurrently with standard chow during Stage 1. This group was euthanized at the end of Stage 1 for baseline pathophysiological assessments.

· **Group III (Ath-NC):** Untreated atherogenic negative control group for evaluating spontaneous recovery. Administered 1 ml/kg b.w./day of AGD during Stage 1, followed by 1 ml of DW during Stage 2.

· **Group IV (Ath-Sv):** Positive chemical treatment control group. AGD (1 ml/kg b.w./day of AGD during Stage 1, followed by simvastatin (0.9 mg/kg b.w./day) dissolved in DW during Stage 2.

· **Group V (Ath-ST):** Sheep tallow treatment group. Administered 1 ml/kg b.w. of AGD orally during Stage 1, followed by 1 ml/kg b.w. of sheep tallow during Stage 2.

· **Group VI (Ath-OO):** Olive oil treatment group. The rats were administered 1 ml/kg b.w. of AGD orally during Stage 1, followed by 1 ml/kg b.w. of olive oil during Stage 2.

2.6. Blood and Tissue Sample Collection

Except for Group II (Ath), which was processed at the end of Stage 1, all dissections and sample collections were performed at the conclusion of Stage 2. Following an overnight fast after the final treatment, blood samples were drawn from the orbital sinus using capillary tubes for biochemical analysis. To estimate plasma fibrinogen, a portion of whole blood was collected in heparinized test tubes (5000 units/ml). The remaining blood was allowed to coagulate at room temperature for 30 min before centrifugation at 2000 rpm for 15 min. The extracted serum was stored at -20℃ for subsequent biochemical analyses. Immediately after blood collection, the animals were euthanized via cervical dislocation. Liver tissues were meticulously excised, rinsed in normal saline, fixed in 10% neutral-buffered formalin for 24 h, and subsequently preserved in 70% ethanol pending histopathological processing.

2.7. Lipid Profile Assay

Serum lipid profiles, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C), were evaluated at baseline, the conclusion of Stage 1, and the conclusion of Stage 2 to continuously monitor hyperlipidemic progression and therapeutic resolution. Analyses were performed using enzymatic colorimetric methods with commercial diagnostic kits (Spinreact Co., Spain) using an RX50V Biochemistry Analyzer (Al-Mageed Medical Lab, Sana'a). The protocols strictly adhered to the manufacturer's operational guidelines. The Atherogenic Index (AI) was derived using the Yokozawa *et al.* equation [30] : AI = TC – HDL/HDL

2.8. Biochemical Analysis of Liver Function and Enzymes

Serum total protein and albumin concentrations were quantified using enzymatic and colorimetric assays with Biolabo Co. kits (France). Globulin levels were calculated algebraically as follows:

Globulin (g/dL)} = Total Protein - Albumin

Plasma fibrinogen levels were concurrently estimated using dedicated Biolabo Co. reagents. The structural integrity of the liver was assessed by measuring the activity of key hepatic enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), using enzymatic colorimetric kits provided by MONLAB Co. (Spain), according to the manufacturer's established protocols.

2.9. Histopathological Analysis

Formalin-fixed liver specimens were dehydrated, embedded, and sectioned to a thickness of 5 μm. Sections were stained with Hematoxylin and Eosin (H&E), strictly adhering to Carson's protocols [31]. Histomorphological evaluations were conducted at 400x magnification utilizing an Olympus CX41 light microscope equipped with a digital photographic interface. An ocular micrometer calibrated with a stage micrometer was used for the quantitative analysis of the liver. The captured images were analyzed using a computerized image analyzer (ImageJ 1.54 /java 1.8.0_345[64- bit]. Each value of the results of the histopathological changes represents the mean of seven rats per group. The frequency of quantitative histopathological changes in each liver section was based on the mean obtained from the observation of three microscope fields $(625\,\mu\mathrm{m}^2)$ at 400x magnification [32].

2.10. Statistical Analysis

Data normality was confirmed across all sets using the Shapiro-Wilk test. Continuous variables are expressed as mean $\pm$ SD . Statistical evaluations were performed using GraphPad Prism software (Version 8.0.2.263, San Diego, CA, USA). Inter-group variance was assessed using a one-way analysis of variance (ANOVA), followed by Tukey's post hoc test to ascertain specific group differences. The threshold for statistical significance was established *a priori* at $P < 0.05$.

3. RESULTS

3.1. Lipid Profile

As illustrated in Fig. 1, the administration of an atherogenic diet (AGD) successfully induced dyslipidemia by the conclusion of Stage 1. This pathogenesis was evidenced by a marked elevation in the serum concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C), concomitant with a reduction in high-density lipoprotein cholesterol (HDL-C) across all atherogenic groups compared to the normal control group.

Following the therapeutic interventions in Stage 2, these disrupted lipid parameters exhibited substantial amelioration in the groups treated with (SV), sheep tallow (ST), and olive oil (OO). Conversely, the untreated atherogenic negative control group (Ath-NC) demonstrated only marginal spontaneous improvements, yielding the lowest recovery among the experimental groups. This stark contrast underscores the pronounced therapeutic efficacy of the administered treatment in resolving dyslipidemia. A comparative analysis of the interventions indicated that olive oil and simvastatin exerted comparable restorative effects on the overall lipid profile, with sheep tallow demonstrating slightly lesser but still considerable efficacy. Notably, the Ath-OO group showed the most substantial increase in HDL-C levels, followed closely by the Ath-ST group. Both lipid-based interventions elevated HDL-C concentrations beyond those observed in the baseline normal (N) and simvastatin-treated (Ath-Sv) groups. Furthermore, the atherogenic index (AI) was reduced to highly comparable levels in both the Ath-Sv and OO groups. The Ath-ST group also exhibited a notable reduction in AI, further confirming its beneficial modulatory effect on hyperlipidemia.

3.2. Hepatic Biochemical Profiles

Compared with the normal control group, the atherosclerotic group (Ath) exhibited a highly significant increase in serum total protein, globulin, and plasma fibrinogen levels ($P < 0.0001$), coupled with a significant decrease in serum albumin concentrations ($P < 0.05$). Following therapeutic interventions, the self-recovery group (Ath-NC) and all treated groups demonstrated a significant restoration of total protein and globulin levels toward baseline values compared to the Ath group. However, no significant modifications were observed in plasma fibrinogen levels among these groups, with the notable exception of the olive oil-treated group (Ath-OO), which showed a statistically significant reduction in fibrinogen levels. Interestingly, although sheep tallow (ST) and olive oil (OO) therapies exerted a more effective corrective influence on the evaluated hepatic proteins than the Ath-NC and Ath-Sv groups, this descriptive trend did not reach statistical significance (Table 1).

The activities of serum hepatic enzymes (ALT, AST, and ALP; Fig. 2) across all experimental groups remained significantly elevated relative to the normal control group. However, when compared directly to the untreated negative control group (Ath-NC), therapeutic intervention with ST precipitated a highly significant attenuation in ALT ($P < 0.0001$) and ALP ($P < 0.001$) activity. Similarly, OO administration markedly downregulated ALT ($P < 0.001$) and AST ($P < 0.0001$) levels. Characteristically, the highest activities of all three evaluated liver enzymes were recorded in the simvastatin-treated group (Ath-Sv), which manifested a profound and substantial elevation in these biomarkers of hepatocellular leakage compared to all other experimental groups.

3.3. Histological Results

3.3.1. Histological sections examination

Histomorphological examination of hepatic cross-sections from the normal control group revealed a healthy, intact liver architecture, characterized by centrally located veins and radiating cords of normal hepatocytes. Hepatocytes exhibited well-preserved cytoplasm and prominent nuclei, along with typical distributions of Kupffer cells (Fig. 3A).

Conversely, hepatic sections from the atherogenic (Ath) group displayed obvious histopathological changes. These included severe disruption of the normal radial cellular arrangement, loss of distinct sinusoids, and extensive parenchymal destruction. The observed structural alterations were characterized by broad areas of cellular degeneration, vacuolization, vasodilation, focal necrosis, irregular portal veins, and evident infiltration of cells (Fig. 3B). Similarly, hepatic tissues from both the untreated negative control (Ath-NC) and simvastatin-treated (Ath-Sv) groups exhibited substantial degenerative changes. The pathological hallmarks in these groups included diffuse fatty changes, prominent vacuolation, vasodilation, microhemorrhages, inflammatory infiltration, vascular congestion, and distinct zones of necrosis populated by pyknotic nuclei (Fig. 3C and Fig. 3D, respectively). In contrast, liver sections from the groups treated with the studied dietary fats, Ath-ST and Ath-OO groups,

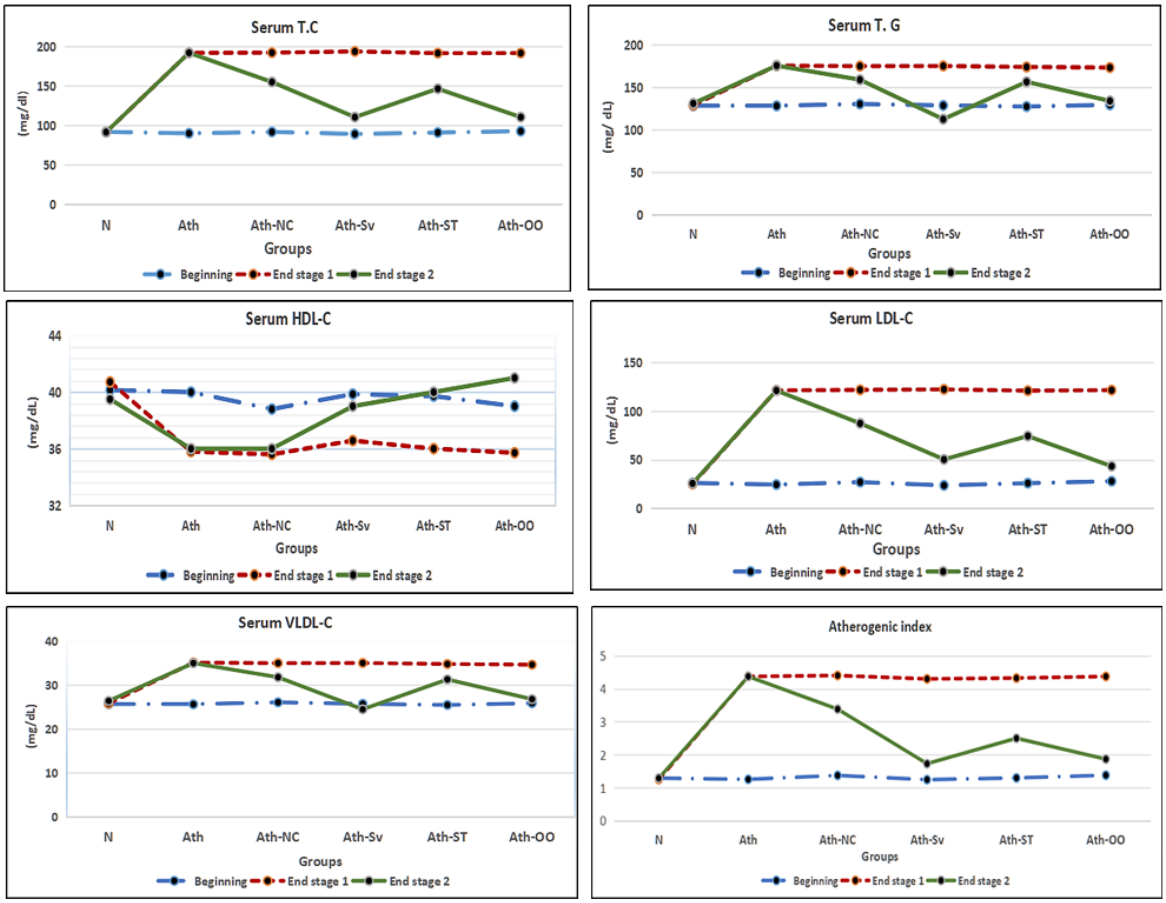

Figure 1. Lipid profile changes across the experimental groups during different stages of the study.

N: Normal; Ath: atherosclerosis; Ath-NC: Ath-Negative control; Ath-Sv: Ath-simvastatin; Ath-ST: Ath-sheep's tallow; Ath-OO: oil-treated atherosclerotic. TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein.

Table 1. Serum levels of Liver protein in the experiment groups

Group / Parameters	N	Ath	Ath-NC	Ath-Sv	Ath-ST	Ath-OO
Total protein (g/dL)	5.50 ± 0.41	8.66 ± 0.39 a ****	6.66 ± 0.09 a **** b ****	6.51 ± 0.15 a **** b ****	6.43 ± 0.10 a **** b ****	6.14 ± 0.21 a ** b ****
Albumin (g/dL)	2.97 ± 0.41	2.32 ± 0.31 a *	2.67 ± 0.19	2.59 ± 0.32	2.66 ± 0.17	2.76 ± 0.24
Globulins (g/dL)	2.53 ± 0.13	6.34 ± 0.43 a ****	3.96 ± 0.11 a **** b ****	3.93 ± 0.32 a **** b ****	3.77 ± 0.14 a **** b ****	3.39 ± 0.36 a ** b ****
Fibrinogen (g/dL)	1.24 ± 0.15	1.69 ± 0.08 a ****	1.59 ± 0.07 a ***	1.64 ± 0.05 a ****	1.47 ± 0.11 a *	1.04 ± 0.15 b **** c **** d ****

Results are shown as mean ± SD for 7 rats in each group.

N: Normal; Ath: atherosclerosis; Ath-NC: Ath-Negative control; Ath-Sv: Ath-Simvastatin; Ath-ST: Ath-Sheep's tallow; Ath-OO: Ath-Olive oil.

The significant differences between groups were judged by ANOVA followed by Tukey's post hoc test as follows: a: significant vs. Normal group; b: significant vs. Ath group; c: significant vs. Ath-NC group; d: significant vs. Ath-Sv group.

* = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$, **** = $P < 0.0001$.

demonstrated remarkable structural recovery and cellular repair compared to the Ath, Ath-NC, and Ath-Sv groups. Both lipid-treated groups exhibited substantial attenuation of hepatic injury, as evidenced by markedly reduced

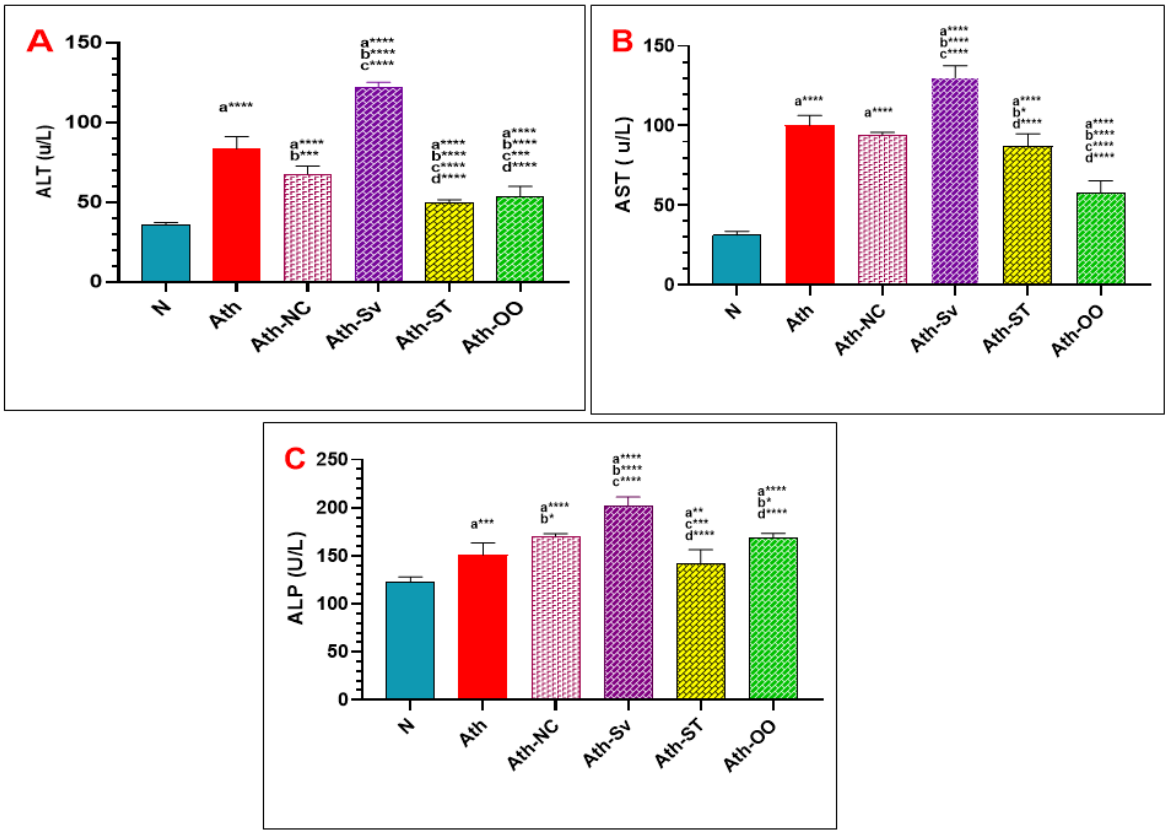

Figure 2. Lipid profile changes across the experimental groups during different stages of the study.

The results are for seven rats in each group. N: Normal, Ath: atherosclerosis; Ath-NC: Ath-negative control; Ath-Sv: Ath-simvastatin; Ath-ST: Ath-sheep's tallow; Ath-OO: Ath-olive oil. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase.
Significant differences between groups were determined using ANOVA followed by Tukey's post hoc test as follows:
a: significant vs. normal group; b: significant vs. Ath- group; c: significant vs. Ath- NC group; d: significant vs. Ath-Sv group. *= P < 0.05, **=P < 0.01, ***=P < 0.001, ****=P < 0.0001

levels of cytoplasmic vacuolation, cellular necrosis, and inflammatory infiltration (Fig. 3E and 3F).

3.3.2. *Quantitative assessment of liver lesions*

Table 2 presents the quantitative histopathological results of most liver lesions observed in the sections, including fatty changes, vacuolation, degeneration, infiltration, inflammation, vasodilation, and necrosis. All lesions in the Ath group showed a highly significant difference ($p < 0.0001$) compared to the normal group, except for infiltration ($p < 0.01$). Most lesions in the Ath NC- and Ath-Sv groups were significantly different from those in the normal group, with the highest scores in vacuolation, degeneration, and necrosis ($p < 0.0001$). Notably, degeneration and infiltration scores were significantly increased ($p < 0.0001$) in the Ath-Sv group compared to the Ath and Ath-NC groups. Additionally, inflammation was significantly higher ($p < 0.001$) in the Ath-Sv group than in the Ath-NC group. The improvement in fatty changes, degeneration, and vasodilation in the Ath- ST and Ath-OO groups compared to the Ath group was highly significant ($p < 0.0001$). However, significant improvements in infiltration ($p < 0.05$) and necrosis ($p < 0.0001$) were observed only in the oil-treated group. Interestingly, the amelioration effects of tallow and olive oil were significant compared to the Ath-Sv and Ath-NC groups for many lesions, with these effects being clearer in the oil-treated group, as shown in Table 2.

4. DISCUSSION

This study aimed to evaluate the therapeutic potential of sheep tallow (ST) and olive oil (OO) in mitigating the hepatic structural and functional alterations associated with atherogenesis [33]. Dyslipidemia, a primary driver of atherosclerosis, was successfully induced using an atherogenic CCT diet (comprising cholesterol, cholic acid, and thiouracil) [29]. This induction subsequently precipitated atherosclerotic lesion formation, corroborated by the distinctive histological evidence found in the aortic sections in our previous study [25]. Following the administration of the atherogenic diet (Stage 1), the serum lipid profiles exhibited marked dysregulation,

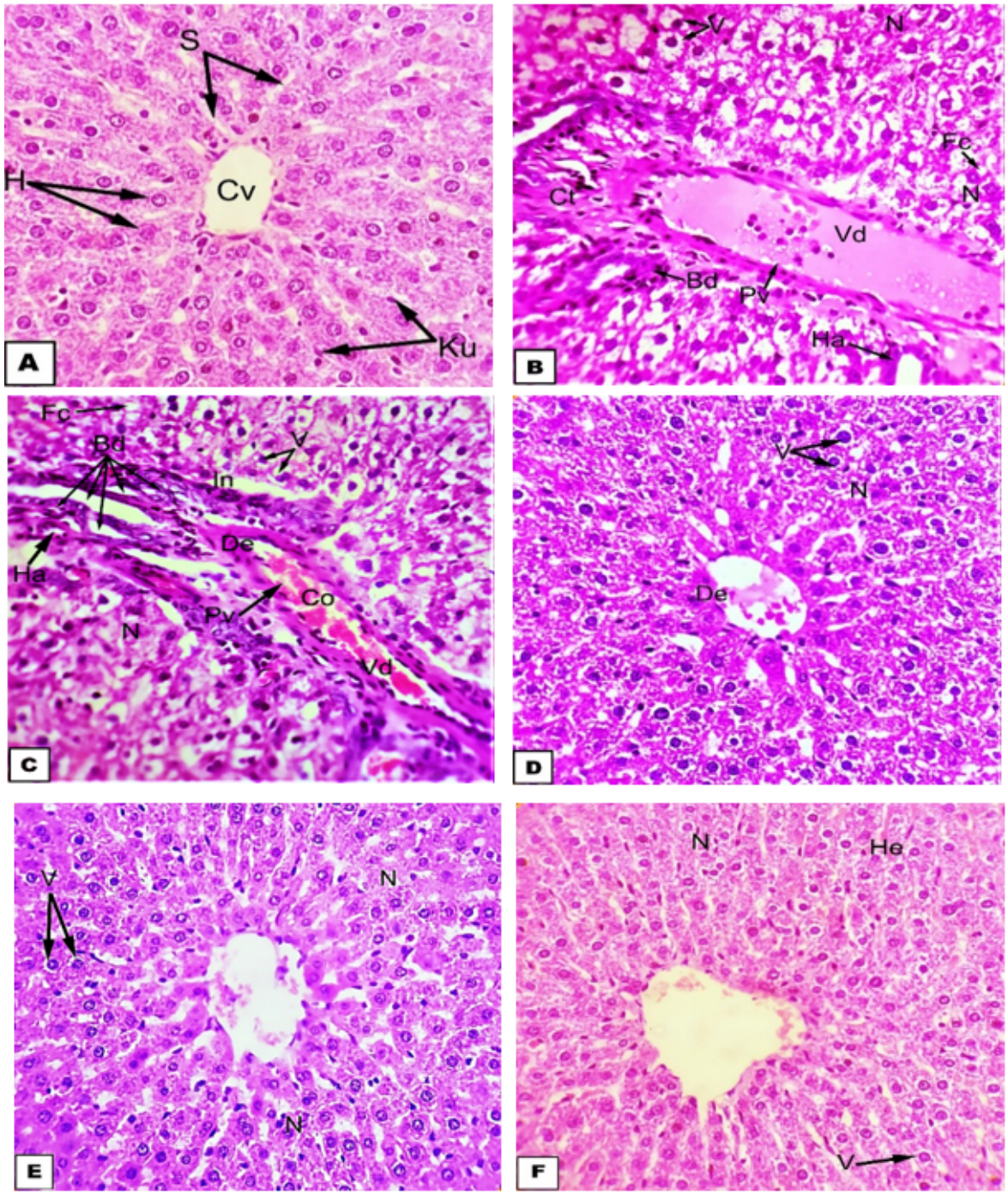

Figure 3. Lipid profile changes across the experimental groups during different stages of the study.

A: Normal group, **B:** Atherogenic group, **C:** Ath-NC group, **D:** Ath-Sv group, **E:** Ath-ST group, **F:** Ath-OO group. (Bd) bile duct, (Ct) connective tissue, (Cv) central vein, (H) hepatocytes, (Ha) hepatic artery, (Ku) Kupffer Cells, (Pv) portal vein, and (S) sinusoids. (Co) congestion, (De) degeneration, (Fc) fatty changes, (In) Infiltration, (Inf) inflammatory, (N) necrosis, (V) vacuolation (Vd) vasodilation (400 ×, H & E stain).

characterized by elevated TC, TG, LDL-C, and VLDL-C levels, alongside diminished HDL-C levels. This result is consistent with that of Zeljkovic *et al.* [9]. High concentrations of LDL-C and TG directly facilitate atherogenesis; these lipids infiltrate the arterial intima, undergo oxidative modifications (forming oxLDL), and induce inflammatory immune responses that drive macrophage recruitment, fatty streak formation, and eventual plaque development [33]. Furthermore, the observed elevation in serum TG and VLDL-C levels may stem from an increased influx of plasma free fatty acids into the liver, thereby upregulating the hepatic synthesis of TG-rich VLDL particles [34]. Following Stage 2 therapeutic interventions, the lipid profiles demonstrated significant recovery. The untreated neg-

Table 2. Quantitative analysis for histopathological lesions of the liver in the experiment groups.

Histopathological lesions	N	Ath	Ath-NC	Ath-Sv	Ath-ST	Ath-OO
Fatty change	+ 0.333 ± 0.153	+++ 23.70 ± 1.709 a****	++ 19.07 ± 1.419 a**** b****	+ 2.300 ± 0.100 b**** c****	+ 1.533 ± 0.153 b**** c****	+ 1.467 ± 0.252 b**** c****
Vacuolation	+ 2.033 ± 0.058	+++ 43.80 ± 0.100 a****	++++ 38.50 ± 1.609 a****	++ 35.57 ± 3.383 a**** b*	++ 25.00 ± 6.767 a**** b****	++ 28.40 ± 0.819 a**** b**** c**
Necrosis	+ 1.267 ± 0.252	++++ 18.80 ± 1.552 a****	++++ 18.23 ± 0.681 a****	++++ 18.87 ± 1.002 a****	+++ 16.6 ± 0.529 a****	+++ 14.00 ± 0.436 a**** b**** c*** d****
Degeneration	- 0.000 ± 0.000	+++ 1.133 ± 0.116 a****	++ 0.933 ± 0.152 a**** b****	++++ 1.933 ± 0.152 a**** b**** c****	+ 0.433 ± 0.153 a** b**** c*** d****	- 0.126 ± 0.000 b**** c**** d****
Infiltration	+ 0.333 ± 0.058	++ 0.867 ± 0.153 a**	++ 0.833 ± 0.058 a*	++++ 2.833 ± 0.208 a**** b**** c****	+ 0.500 ± 0.100 d****	+ 0.367 ± 0.153 b* c* d****
Inflammation	+ 0.067 ± 0.058	++++ 1.200 ± 0.264 a****	++ 0.633 ± 0.058 a** b**	++++ 1.333 ± 0.153 a**** b**** c***	+ 0.200 ± 0.200 b**** d****	+ 0.067 ± 0.058 b**** c** d****
Vasodilation	+ 0.167 ± 0.153	+++ 2.167 ± 0.251 a****	++ 1.100 ± 0.200 a** b***	++ 1.533 ± 0.153 a****	+ 0.400 ± 0.000 b**** c* d***	+ 0.133 ± 0.058 b**** c** d****

Results are shown as mean ± SD for 7 rats per group.

N: Normal; Ath: atherosclerosis; Ath-NC: Ath–Negative control; Ath-Sv: Ath–Simvastatin; Ath-ST: Ath–Sheep's tallow; Ath-BT: Ath–Bovine's tallow; Ath-OO: Ath–Olive oil.

The significant differences between groups were judged by ANOVA followed by Tukey's post hoc test as follows: a: significant vs. normal group; b: significant vs. Ath. group; c: significant vs. Ath-NC group; d: significant vs. Ath-Sv group.

* = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$, **** = $P < 0.0001$.

Grades are as follows: (-) absent; (+) trace (1–25%); (++) weak (26–50%); (+++) moderate (50–75%); (++++) severe (75–100%).

ative control (Ath-NC) exhibited the least improvement, underscoring the efficacy of the administered treatments in modulating dyslipidemia in mice. Both OO and ST interventions effectively restored lipid parameters, with OO exhibiting a restorative capacity comparable to that of the pharmacological standard simvastatin. As previously determined via GC/FID analysis [25], the hypolipidemic properties of ST and OO are fundamentally linked to their specific fatty acid profiles, which favor lipid homeostasis. Both fats contain stearic acid, which has been shown to exert beneficial effects by lowering plasma cholesterol and LDL-C levels [35]. Moreover, OO possesses a higher proportion of oleic and trans-linoleic acids than ST; this elevated monounsaturated fatty acid (MUFA) content, particularly oleic acid, is widely recognized for its capacity to reduce LDL-C and mitigate overall cardiovascular risk [36, 37]. Additionally, the presence of lauric acid in both ST and OO likely contributed to the observed increase in HDL-C levels [38]. Crucially, HDL-C concentrations in the Ath-OO and Ath-ST groups surpassed those in both the normal baseline and simvastatin-treated groups. Functionally, HDL-C maintains cellular lipid homeostasis, prevents intimal foam cell formation, and mediates reverse cholesterol transport by facilitating cholesterol efflux from peripheral macrophages to the liver for excretion [39]. Furthermore, ST provides short-chain fatty acids (SCFAs), such as butyric, capric, and caprylic acids [25]. These SCFAs are known to enhance lipid and glucose metabolism [40], and caprylic acid has been shown to reduce lipid accumulation and attenuate atherosclerosis [41]. Consequently, the evaluation of the atherogenic index revealed that OO most effectively preserved the lipid balance, followed closely by ST, affirming their marked ameliorative effects on dyslipidemia. This study highlights the close interrelationship between systemic lipid profiles and hepatic pathophysiology. Atherosclero-

sis inherently disrupts hepatic protein synthesis, driving the upregulation of pro-atherogenic apolipoproteins while suppressing their protective counterparts [42]. Elevated hepatic ApoB production in hyperlipidemic states facilitates the assembly and secretion of atherogenic VLDL particles, which readily oxidize and infiltrate vessel walls [43, 44]. Diminished liver-derived ApoA1 impairs HDL-mediated cholesterol efflux, accelerating foam cell formation [43, 44]. Biochemically, the atherogenic (Ath) group exhibited highly significant increases ($P < 0.0001$) in total serum protein, globulin, and fibrinogen levels, alongside a marked reduction ($P < 0.05$) in albumin levels. While these findings align with some studies detailing hyperlipidemia-induced protein alterations [45], they contrast with others reporting broad decreases in total protein, albumin, and globulin [46]. Plasma protein profiles serve as critical biomarkers for atherosclerosis progression and cardiovascular risk, reflecting systemic inflammation, oxidative stress, and altered hepatic function [47]. Hypoalbuminemia and hyperglobulinemia are established clinical indicators of atherogenesis [48]. Although advanced atherosclerosis typically features reduced total plasma protein due to cytokine-driven (e.g., IL-6, TNF-a) protein catabolism [49], the significant increase in total protein observed in the Ath group likely reflects an early stage acute-phase response. Initial plaque formation stimulates the hepatic overproduction of acute-phase reactants (such as fibrinogen and CRP), causing a transient elevation in total protein levels prior to the onset of dominant hypoalbuminemia [25, 49]. The significant decline in albumin further underscores the inflammatory suppression of hepatic transcription, potentially exacerbated by glycation or urinary loss in nephropathy [50, 51]. Concomitantly, the elevated fibrinogen levels observed in the Ath group act as potent mediators of early plaque formation by enhancing platelet aggregation and reactivity [52]. Hepatic biosynthesis of hepcidin is heavily upregulated during inflammation by acute-phase cytokines, primarily IL-6 [53, 54]. Likewise, the hyperglobulinemia noted in the Ath group reflects an acute-phase elevation of alpha, beta (including fibrinogen), and gamma (including CRP) globulins [55]. Three months of AGD administration significantly elevated serum hepatic enzymes (ALT, AST, and ALP) and produced pronounced histopathological lesions, including fatty changes, vacuolation, degeneration, cellular infiltration, and necrosis. These elevations directly correlate with the severity of hepatic tissue damage, as aminotransferases are highly specific indicators of hepatocellular injury, plasma membrane disruption and apoptosis [56, 57]. Our findings are consistent with previous reports of elevated ALT and AST levels in hyperlipidemic rat models [58, 59]. An increase in ALT primarily indicates hepatic inflammation or injury, whereas elevated AST suggests broader hepatic dysfunction or concomitant myocardial cell injury [60]. Furthermore, increased transaminase levels may reflect impaired lipoprotein metabolism [61], and elevated ALP levels are strongly associated with increased atherosclerotic risk, particularly in inflammatory conditions [62]. Notably, the simvastatin-treated group exhibited severe enzymatic elevation and pronounced tissue lesions, consistent with clinical observations linking statin therapy to hepatotoxicity [63]. This adverse hepatic effect may be mediated by the stimulation of cytochrome P450 enzymes, which generate hepatotoxic free radicals and electrophiles [64, 65]. The histological deterioration observed in the atherogenic groups can be largely attributed to intracellular lipid accumulation and severe oxidative stress [66]. In our companion study [25], AGD-fed rats were found to have increased serum malondialdehyde (MDA), a potent indicator of lipid peroxidation (LPO). Increased MDA disrupts membrane permeability and amplifies reactive oxygen species (ROS) production, which overwhelms cellular antioxidant defenses and precipitates structural hepatocyte damage [59, 67]. Furthermore, the ensuing cellular necrosis is likely exacerbated by depleted mitochondrial glutathione, a critical regulator of mitochondrial ROS and cellular apoptotic pathways [68]. Conversely, the administration of ST and OO in the current study, which has previously been shown to be non-toxic to hepatic function in healthy experimental rats [69], markedly attenuated AGD-induced hepatic injury in rats. Fat administration successfully attenuated the increases in serum liver enzymes, total protein, globulin, and fibrinogen levels and recovered albumin concentrations. This biochemical normalization is likely linked to the reduction of inflammatory markers and MDA, alongside enhanced total antioxidant capacity, as found in our previous study [25]. Additionally, these treatments may counteract the catabolic effects of stress-related hormones, such as cortisol and glucagon [70]. The hepatoprotective properties of OO and ST observed in this study are intrinsically linked to their fatty acid composition. MUFAs, particularly oleic acid (abundantly present in OO and moderately in ST), exert potent anti-inflammatory effects, improve endothelial function, and attenuate hepatocellular lipotoxicity *in vitro* and *in vivo* [25, 71, 72]. Furthermore, the SCFAs in ST, including butyric, capric, and caprylic acids, provide considerable anti-inflammatory, immunoregulatory, cardioprotective, and mitochondrial-supporting benefits [25, 72–74]. Beyond their fatty acid profiles, both fats are rich in essential nutrients and bioactive compounds, such as -tocopherol and other fat-soluble vitamins [75, 76]. Additionally, the diverse structural components in extra virgin olive oil, including phenolic compounds, sterols, and hydrocarbons [77], work synergistically to protect cellular structures from oxidative damage and promote strong anti-inflammatory effects, thereby restoring liver health and overall physiological balance. Unlike our findings on sheep tallow, Al-Mayyahi et al. [78] showed that a tallow diet negatively affected lipid levels and liver enzymes, and it also caused liver histopathological changes similar

to non-alcoholic fatty liver disease, with a diet containing 20% fat. However, our experiment used only 1 ml/kg of sheep tallow; this difference in ST dosage is probably why the results differ. This study has limitations and requires further complementary studies utilizing molecular markers, inflammatory cytokines, and varying doses, as well as long-term follow-up.

5. CONCLUSION

This study substantiates the therapeutic efficacy of olive oil and sheep tallow in rectifying dyslipidemia and restoring blood lipid profiles disrupted by an atherogenic diet in experimental rats. Furthermore, the findings highlight the hepatoprotective properties of specific dietary fats. Both interventions successfully ameliorated atherosclerosis-associated hepatic dysfunction, as evidenced by the normalization of serum liver protein profiles and significant attenuation of hepatocellular degeneration, tissue injury, and elevated hepatic enzyme activities. The results of this study provide new preliminary evidence regarding the beneficial effects of the investigated dietary fats on the lipid profile, liver structure, and liver function. However, further research is required to validate and expand these findings. Future studies focusing on the underlying molecular and cellular mechanisms, together with dose–response evaluations, are warranted to elucidate these pathways. Such advanced research will be critical for exploring the broader health applicability of lipid-based interventions in managing diverse physiological and anatomical pathologies, particularly those compromising the liver's central role in maintaining systemic homeostasis.

Declarations

Ethical Approval

This study protocol was approved by the "Committee of Experimental Animal Care and Use," Faculty of Science, Sana'a University, Yemen (ethical code: BAHSS 101).

Conflict of interest

The authors declare no competing interests.

Competing interests

The authors have no financial or proprietary interest in any material discussed in this article.

Authors' contributions

All authors contributed to the study's conception and design. All authors performed the experiments, data analysis, and wrote and commented on the present version of the manuscript. All the authors have read and approved the final manuscript.

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Availability of data and materials

No datasets are used in the present study.

Consent for publication

The authors confirm that informed consent was obtained for the publication of the data contained in this article.

Consent to participate

Informed consent was obtained from all authors.

Declaration of AI-Assisted Technologies

"The authors declare that artificial intelligence (AI) tools were used only for limited purposes, such as language editing, grammar improvement, and formatting assistance. All scientific content, data analysis, interpretations, conclusions, and final manuscript revisions were reviewed and verified by the authors, who took full responsibility for the integrity and originality of the work."

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