

Short Communication

Exogenous Ganglioside GM1 Exacerbates Atherosclerosis in apoE^{-/-} Mice Fed a High-Fat Diet

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Abstract

Background: Atherosclerotic cardiovascular diseases (ASCVDs) are leading causes of mortality and disability worldwide. Endogenous monosialotetrahexosylganglioside (ganglioside GM1), a major component of cell membrane lipid rafts, plays an important role in atherogenesis. However, the specific *in vivo* effects of exogenous GM1 on atherosclerosis remain poorly understood. **Methods:** To investigate these effects, an atherosclerotic model was established using apolipoprotein E-deficient (apoE^{-/-}) mice fed a high-fat diet (HFD) for 12 weeks. The treatment group received intravenous injections of GM1 (7.5 mg/kg) *via* the tail vein once every 3 days, whereas the apoE^{-/-} HFD group received phosphate-buffered saline (PBS). Disease progression was evaluated by monitoring body and liver weights, measuring systemic lipid levels, and quantifying atherosclerotic plaque areas in the aortic arch, whole aorta, and aortic root. **Results:** Exogenous GM1 treatment significantly increased atherosclerotic plaque formation in the whole aorta and aortic root compared with the apoE^{-/-} HFD group. This effect occurred without increases in total cholesterol (TCH), low-density lipoprotein-cholesterol (LDL-C), or high-density lipoprotein cholesterol (HDL-C) levels, whereas plasma triglyceride (TG) levels were significantly reduced. **Conclusions:** Exogenous ganglioside GM1 exacerbated atherosclerosis in apoE^{-/-} mice, contrasting with the previously reported atheroprotective effects of its precursor, monosialodihexosylganglioside (GM3). Although the mechanisms underlying this effect remain unclear, potentially involving direct vascular signalling or alterations in lipid raft composition, these findings support further investigation of the role of GM1 and its metabolic pathways as critical targets for further research in atherosclerosis biology.

Keywords: ganglioside GM1; ganglioside GM3; atherosclerosis; apoE-deficient mouse; lipid raft

1. Introduction

Atherosclerosis (AS) is a chronic inflammatory vascular disease characterized by the lipid deposition-induced thickening of the arterial wall and narrowing of the vessel lumen [1,2,3]. Atherosclerotic cardiovascular diseases (ASCVDs), including stroke, coronary artery disease (CAD), and peripheral arterial diseases, are the leading causes of disability and death worldwide, resulting from thrombotic vessel occlusion, ischemia, and infarction of the heart, brain, and extremities, respectively. Many risk factors, including low-density lipoprotein-cholesterol (LDL-C), oxidized LDL (oxLDL), and aggregated LDL (agLDL), as well as diagnostic biomarkers, including microRNAs and extracellular vesicles (EVs), have been identified [4,5,6,7]. Identifying influential factors with anti-atherosclerotic or pro-atherosclerotic effects may help facilitate the development of novel strategies for the diagnosis and/or treatment of atherosclerosis.

Gangliosides are a large family of glycosphingolipids (GSLs) containing one or more sialic acid residues that play

diverse roles in diseases, including serving as early diagnostic and prognostic markers, targets for therapy, enhancers of immunotherapy, and components of drug delivery systems [8,9,10,11,12]. Recently, exogenous monosialodihexosylganglioside GM3 (ganglioside GM3), the simplest member of the glycosphingolipid family and a precursor of other complex gangliosides, was shown to exert anti-atherosclerotic effects [13,14]. Moreover, pH-responsive GM3 delivery using reconstituted high-density lipoprotein (rHDL) has been shown to enhance its anti-atherosclerotic effects [15]. Furthermore, GM3-rHDL can serve as a novel nanocarrier for delivering other anti-atherosclerotic drugs such as statins, thereby further enhancing their *in vivo* anti-atherosclerotic efficacy [16].

Ganglioside GM1 is a complex monosialoganglioside derived from GM3 and belongs to the α -series gangliosides. It has also been reported that GM1 modification enhances the anti-atherosclerotic efficacy of statin-loaded rHDL in atherosclerotic model mice [17]. These findings raise the possibility that the anti-atherosclerotic effects of exogenous



GM3 may be mediated, at least in part, by GM1 generated through the metabolism of exogenous GM3 in cells. To address this question, this study investigated the effects of exogenous GM1 on atherosclerosis in apolipoprotein E-deficient (apoE^{-/-}) mice fed a high-fat diet (HFD).

2. Materials and Methods

2.1 Materials and Reagents

Exogenous ganglioside GM1 (purity: 97–100%) was supplied by Shanghai Macklin Biochemical Co., Ltd (Shanghai, China, Cat. No. G873919). GM1 was solubilized in phosphate-buffered saline (PBS) for *in vivo* experiments. Enzymatic assay kits for triglyceride (TG, Cat. No. TG00011), total cholesterol (TCH, Cat. No. TCH0011), high-density lipoprotein-cholesterol (HDL-C, Cat. No. HDL0011), and LDL-C (Cat. No. LDL0011) were purchased from Anhui Iprocom Biotechnology Co., Ltd (Hefei, China). Oil Red O was purchased from Solarbio Life Sciences Co., Ltd (Beijing, China, Cat. No. O8010).

2.2 Animals and Treatment

To establish the atherosclerotic mouse model, male apoE^{-/-} C57BL/6 mice (8-week-old; Beijing Vital River Laboratory Animal Technology Co., Ltd., Beijing, China) were fed a high-fat, high-cholesterol diet (basic forage supplemented with 21% fat, 0.15% cholesterol; Human SJA Lab Animal Ltd., Changsha, China). Mice were housed under specific pathogen-free conditions at 20–24 °C and 40–70% relative humidity under a 12-h light/dark cycle, with free access to food and water. All procedures were performed in compliance with relevant laws and institutional guidelines, and all animal experiments were approved by Jiangxi University of Chinese Medicine Health Research Ethics Board (Reference No. JZLLSC2019-0255; approval date: Dec. 30, 2019).

After 1 week of acclimatization, all apoE^{-/-} mice (n = 21) were randomly divided into three groups (n = 7 in each group): The control group, apoE^{-/-} HFD group, and GM1 treatment group. The individual mouse was considered the experimental unit. The sample size (n = 7 per group) was determined based on our previous study [13] and considerations of animal welfare and minimizing animal use; no formal a priori sample size calculation was performed. The control group was fed a normal chow diet for 12 weeks; the apoE^{-/-} HFD group was fed an HFD for 12 weeks; and the GM1 treatment group was fed an HFD for 12 weeks. Meanwhile, GM1 solutions (150 µL; 7.5 mg/kg) in PBS were administered once every 3 days intravenously via tail vein injection. No a priori inclusion or exclusion criteria were established. All 21 animals enrolled in the study were included in the final analyses, and no animals or data points were unexpectedly excluded. No adverse events related to the experimental procedures were observed during the study.

In our previous study, the highest GM3 dosage of 4 mg/kg produced the greatest anti-atherosclerotic effect [13]. Considering the higher molecular weight of GM1 (~1564) compared with GM3 (~1180), a dose of 7.5 mg/kg GM1 corresponds to approximately 4.8 µmol/kg, which is slightly higher on a molar basis than the 4 mg/kg GM3 dose (3.4 µmol/kg). This GM1 dosage (7.5 mg/kg) is slightly lower than the previously reported GM1 dose of 10 mg/kg administered intraperitoneally or intramuscularly to rats [18,19]. Therefore, to minimize animal use in accordance with animal ethics principles, only one GM1 treatment group receiving 7.5 mg/kg was included in this study. Blinding procedures for atherosclerotic plaque quantification are described in Section 2.4.

At the end of treatment, the mice were weighed and sacrificed. Inhalation anesthesia was performed using a Taiji small animal anesthesia machine (RWD Life Science, Shenzhen, Guangdong, China). The mice were induced with 3–4% isoflurane (RWD Life Science) and maintained at 1.5–2.0% with an appropriate oxygen flow rate (1.0 L/min). At the endpoint, animals were euthanized via CO₂ asphyxiation, and death was confirmed by cardiac arrest in accordance with institutional animal care protocols. Tissue samples were then harvested for subsequent analysis, and the livers were weighed.

2.3 Blood Lipid Profiling

The blood samples in EDTA-containing Eppendorf tubes were centrifuged at 3000 rpm for 10 minutes, and the supernatants were collected for further lipid profiling. Commercial kits (Anhui Iprocom Biotechnology Co., Ltd.) and an automatic biochemical analyzer (AU480; Beckman Coulter, Brea, CA, USA) were used to measure the blood concentrations of TG, LDL-C, and HDL-C at 546 nm and TCH at 505 nm according to the manufacturer's instructions.

2.4 Observation and Quantification of Atherosclerotic Plaques at Different Locations of the Aorta

The observation and quantification of atherosclerotic plaques were performed as previously reported [20]. After blood collection and perfusion, atherosclerotic plaques in the mouse aortic arches were immediately imaged *in situ*. The whole aorta and heart from each mouse were collected and treated separately as follows. The whole aorta was fixed in 4% paraformaldehyde and opened longitudinally. After staining with Oil Red O in propylene glycol, the whole aorta was washed with 60% propylene glycol and examined. Hearts, including the aortic roots, were fixed in 4% paraformaldehyde for 48 hours, dehydrated in 30% sucrose, embedded in an optimal cutting temperature compound, and serially sectioned at a thickness of 7 µm using a cryotome. Following fixation with 95% ethanol, the sections were stained with Oil Red O and hematoxylin, and subsequently visualized. Plaque area quantification was

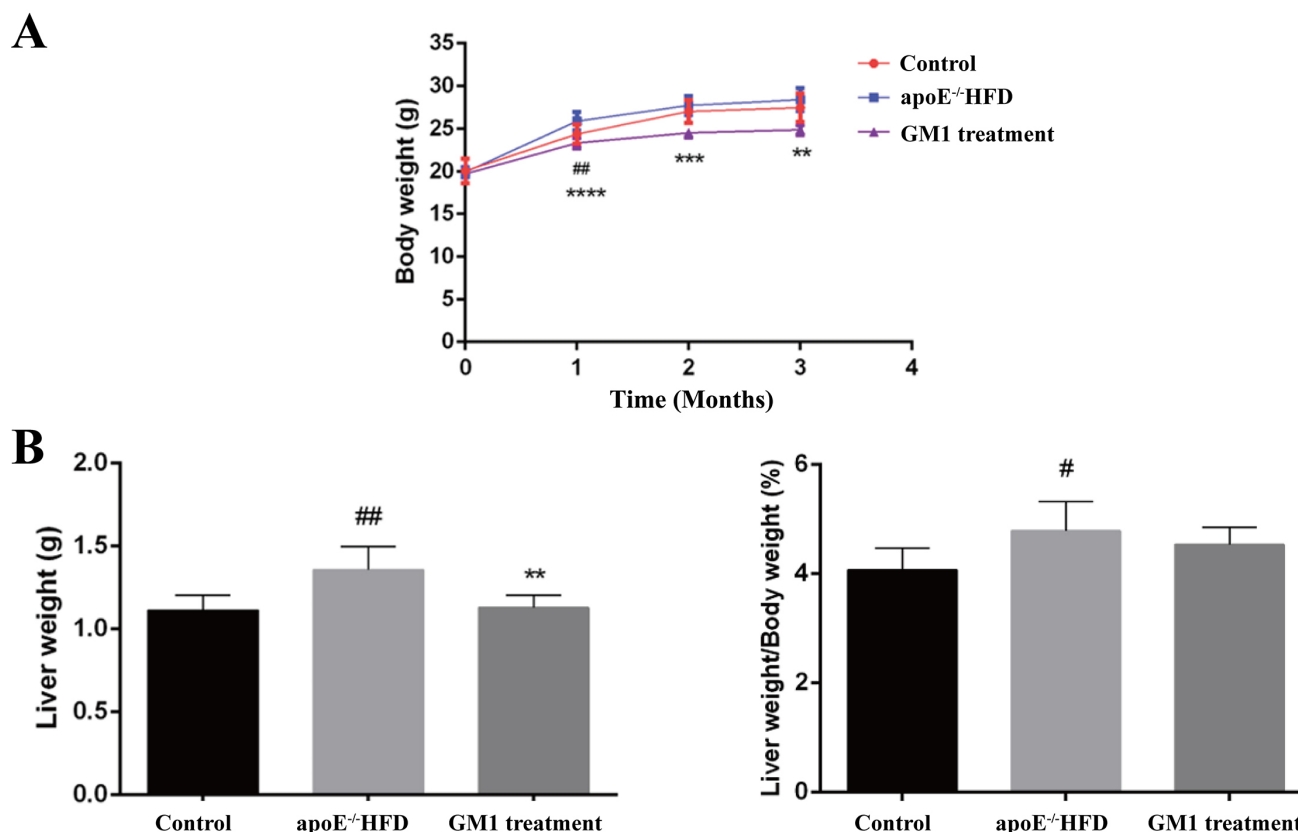


Fig. 1. Effects of exogenous ganglioside GM1 on body weight and liver weight in apoE^{-/-} mice. (A) Changes in mouse body weight over the 12-week experimental period. (B) Absolute liver weight (left panel) and the ratio of liver weight to body weight (right panel) at the end of the study. Data are presented as the mean $\pm$ SEM ($n = 7$ per group). The apoE^{-/-} HFD group received an HFD and PBS. The GM1 treatment group received an HFD and GM1 (7.5 mg/kg). #, $p < 0.05$ and ##, $p < 0.01$ compared with the control group; **, $p < 0.01$, ***, $p < 0.001$ and ****, $p < 0.0001$ compared with apoE^{-/-} HFD. ganglioside GM1, endogenous monosialotetrahexosylganglioside; apoE^{-/-}, apolipoprotein E-deficient; SEM, standard error of the mean; HFD, high-fat diet; PBS, phosphate-buffered saline.

performed by an investigator blinded to group allocation. For quantitative analyses, the percentage of atherosclerotic plaque (i.e., positively stained red lesions) relative to the total area of the aortic root or the total area of the whole length aorta in each image was measured and calculated using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

2.5 Statistical Analyses

All experimental results are expressed as the mean $\pm$ standard error of the mean (SEM). GraphPad Prism software (La Jolla, CA, USA) was applied for data analyses. Statistical analyses were performed using Student's *t*-test and one-way analysis of variance (ANOVA) to assess statistical significance between two groups and among multiple groups, respectively. For all analyses, $p < 0.05$ between two groups was considered statistically significant.

3. Results and Discussion

In this study, apoE^{-/-} mice were randomly divided into three groups: the control group, which was fed a normal

chow diet for 12 weeks; the apoE^{-/-} HFD group, which was fed an HFD for 12 weeks; and the exogenous GM1 group, which was fed an HFD and intravenously administered GM1 solution (150 μ L; 7.5 mg/kg) in PBS once every 3 days for 12 weeks. Over the 12 weeks, the average body weight of mice in the apoE^{-/-} HFD group slightly increased compared with that of the control group. However, the exogenous GM1 treatment significantly decreased the average body weight of mice compared with the apoE^{-/-} HFD group (Fig. 1A). At the end of the 12 weeks, the average liver weight of mice in the apoE^{-/-} HFD group was significantly higher than that of the control group. Although exogenous GM1 treatment significantly decreased the average liver weight of mice compared with the apoE^{-/-} HFD group (left panel of Fig. 1B), it did not significantly alter the liver weight-to-body weight ratio in HFD-fed mice (right panel of Fig. 1B). In other words, exogenous GM1 treatment did not significantly alter liver weight-to-body weight ratio in HFD-fed mice, accounting for changes in body weight.

Next, blood lipid profiling (Fig. 2) showed that the HFD significantly increased cholesterol levels in the

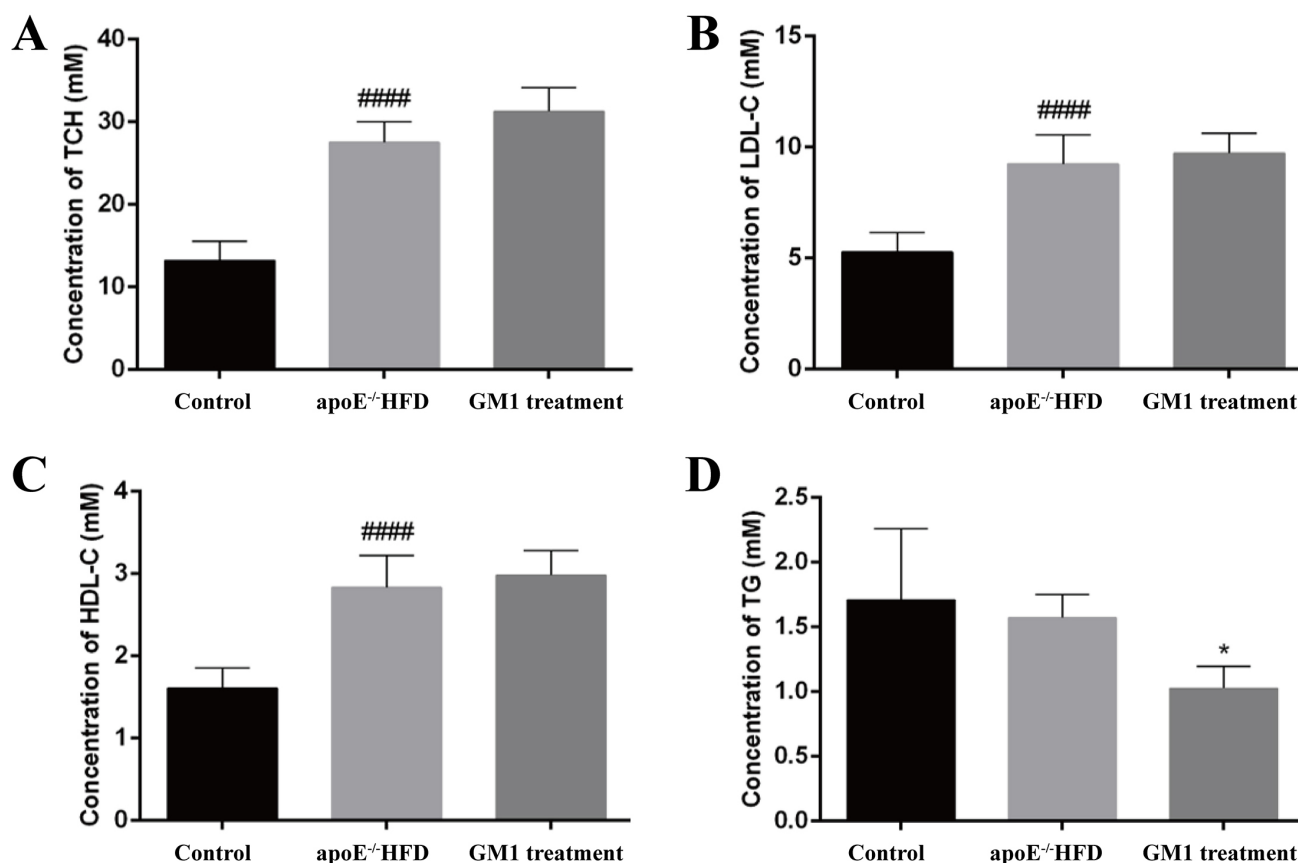


Fig. 2. Effect of exogenous ganglioside GM1 on blood lipid profiles. (A) Total cholesterol (TCH). (B) low-density lipoprotein-cholesterol (LDL-C). (C) high-density lipoprotein-cholesterol (HDL-C). (D) triglyceride (TG). Blood samples were collected at the end of the 12-week treatment. Data are presented as the mean $\pm$ SEM ($n = 7$ per group). ####, $p < 0.0001$ compared with the control; *, $p < 0.05$ compared with the apoE^{-/-} HFD group.

apoE^{-/-} HFD group, including TCH, LDL-C, and HDL-C, further supporting the successful establishment of the atherosclerotic model. Surprisingly, exogenous GM1 treatment did not alter cholesterol levels, including TCH, LDL-C, and HDL-C (Fig. 2A–C), but significantly reduced TG levels (Fig. 2D). These findings suggest that exogenous GM1 may influence hepatic triglyceride metabolism rather than cholesterol metabolism.

Subsequently, atherosclerotic lesions in the arteries were evaluated. Histological imaging (Fig. 3) clearly showed that, compared with the control group, HFD feeding induced the formation of prominent atherosclerotic lesions in the aortic arch, whole aorta, and aortic root (middle images of Fig. 3A–D, respectively), indicating the successful establishment of the atherosclerotic mouse model. Compared with the apoE^{-/-} HFD group, interestingly, exogenous GM1 treatment resulted in substantially more atherosclerotic plaques in the aortic arch (right panel of Fig. 3A; plaques indicated by red arrows), the whole aorta stained with Oil Red O (right panel of Fig. 3B), and the aortic root stained with hematoxylin and eosin (right panel of Fig. 3C) or Oil Red O (right panel of Fig. 3D). Sta-

tistical analyses (Fig. 4) further confirmed that exogenous GM1 significantly exacerbated the HFD-induced increase in atherosclerotic lesion area in both the whole aorta (Fig. 4A) and aortic root (Fig. 4B).

Here, we surprisingly found that exogenous GM1 exerts a pro-atherosclerotic effect on apoE^{-/-} HFD mice (Figs. 3,4), in contrast to the anti-atherosclerotic effect of exogenous GM3 [13]. Based on the lipid profiling data (Fig. 2), the pro-atherosclerotic effect of exogenous GM1 did not appear to result from alterations in plasma cholesterol levels or hepatic cholesterol metabolism, suggesting that exogenous GM1 may exert its pro-atherosclerotic effects by directly acting on atherosclerotic plaques. The opposing effects of GM1 and GM3 on atherosclerosis also suggest that the previously reported anti-atherosclerotic effect of exogenous GM3 was likely not mediated by GM1 generated through the metabolism of exogenous GM3.

Atherosclerosis is a complex systemic disease driven by interconnected pathways, including cholesterol homeostasis, immune responses, inflammation, and oxidative stress [21]. Furthermore, lipid metabolism and disease progression are regulated by complex network-level inter-

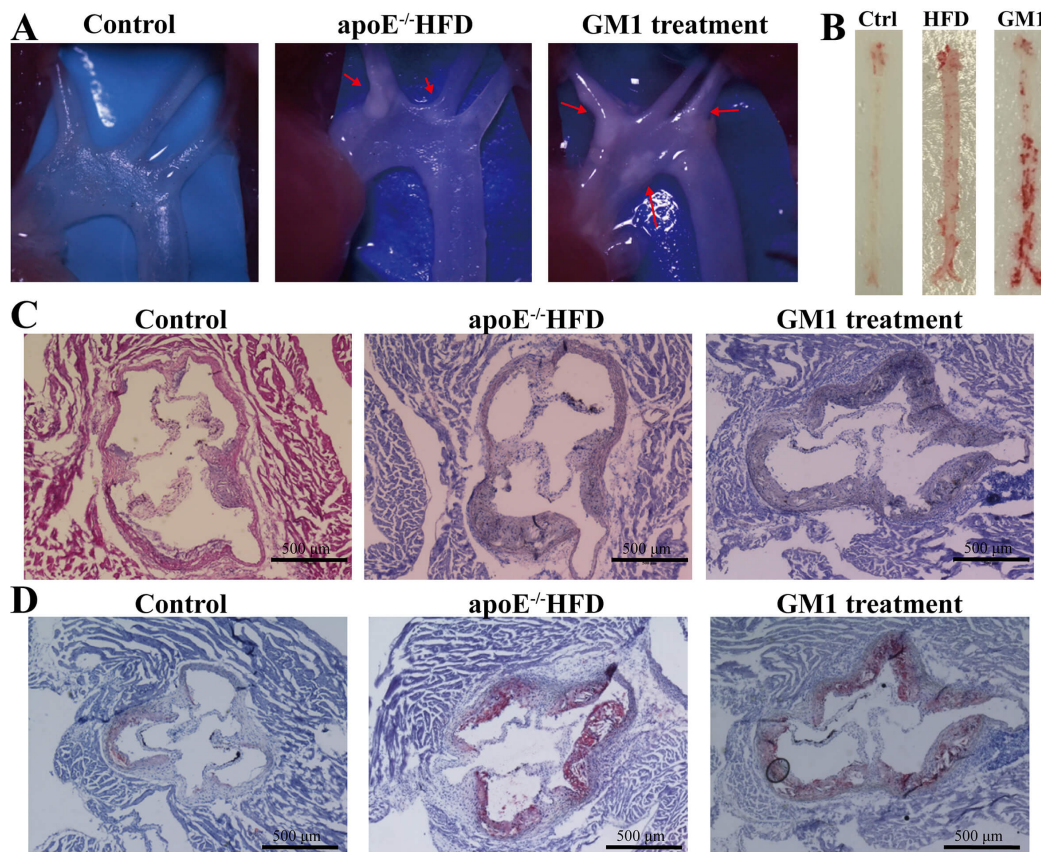


Fig. 3. Representative macroscopic and microscopic images of atherosclerotic plaques. (A) Macroscopic observation of the aortic arch. Red arrows indicate atherosclerotic lesions. (B) En face images of the whole aorta stained with Oil Red O for lipid deposition. (C) Representative cross-sectional microscopic images of the aortic root stained with hematoxylin and eosin. (D) Representative cross-sectional microscopic images of the aortic root stained with Oil Red O. Scale bars represent 500 μm.

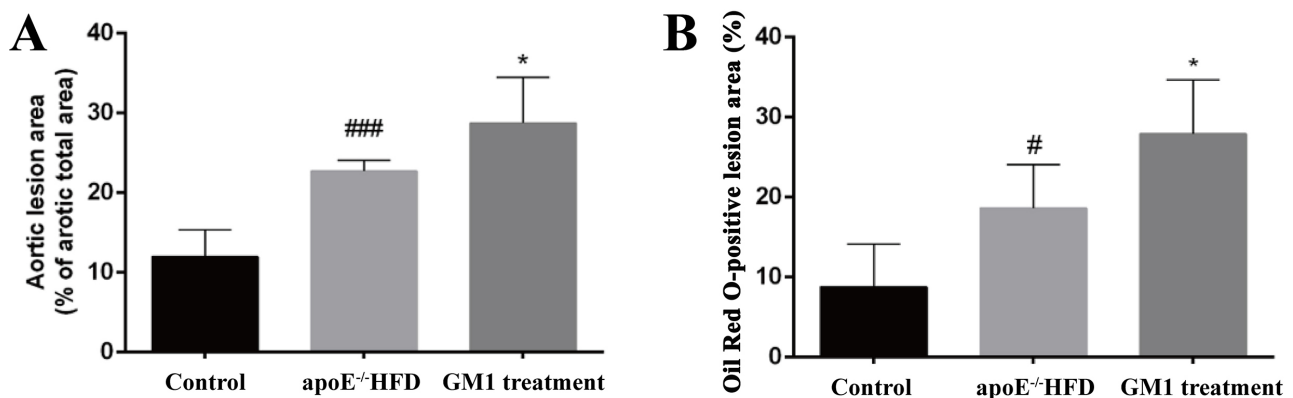


Fig. 4. Quantitative analyses show the effect of exogenous ganglioside GM1 on atherosclerotic plaques. (A) Quantitative analysis of the atherosclerotic lesions in the whole aorta of mice stained with Oil Red O. (B) Quantitative analysis of the atherosclerotic lesions in the aortic root of mice stained with Oil Red O. Data are presented as the mean ± SEM (n = 7 per group). #, $p < 0.05$ and ###, $p < 0.001$ compared with the control; *, $p < 0.05$ compared with the apoE^{-/-} HFD group.

actions [22]. Lipid rafts serve as critical platforms for signal transduction across diverse cellular processes [23]. Therefore, the pro-atherosclerotic effect of exogenous GM1 should be interpreted within this broader biological context. Exogenous GM1 might alter local signaling in lipid rafts.

These alterations could subsequently influence downstream inflammatory pathways or oxidative stress networks in the vascular wall. Understanding these complex interactions will provide a more comprehensive view of ganglioside biology in atherosclerosis.

The underlying mechanisms responsible for the opposing effects of exogenous GM1 and GM3 on atherosclerosis remain unclear. It is well known that GM1 and GM3 are major markers of lipid rafts, also known as membrane rafts. These nanometer-sized microdomains in cellular membranes are composed primarily of cholesterol, glycosphingolipids, and specific proteins and play critical roles in various cellular activities, including serving as platforms for signaling pathways [23,24,25]. Interestingly, GM1 (or GM1 rafts) and GM3 (or GM3 rafts) are generally localized to opposite regions of the plasma membrane in an apical-basolateral manner (i.e., at the apical and basolateral membranes of epithelial cells, respectively [26,27]), a leading-edge-uropod manner (i.e., at the leading edge and uropod of migrating activated lymphocytes for GM3 and GM1, respectively [28]), or a peak-valley manner (i.e., at the peaks and valleys of cell membrane fluctuations for GM3 and GM1, respectively [29]), and mediate different signaling pathways. Therefore, the opposing effects of exogenous GM1 and GM3 on atherosclerosis seem reasonable and are not entirely surprising, although the mechanism underlying the effect of endogenous GM1 on atherosclerosis remains unclear. Further in-depth studies, including investigations into the role of GM1 rafts in atherosclerosis, are needed to elucidate the underlying molecular mechanisms. The pro-atherosclerotic effect of GM1 suggests that GM1 or its related metabolic enzymes may represent potential therapeutic targets for the treatment of atherosclerosis.

4. Limitations

This study had several limitations. First, the small sample size ($n = 7$ per group) may have limited the statistical power of the study. Second, we used a single, fixed dose of GM1 and therefore could not evaluate dose-dependent effects. Third, we focused on plaque area but did not perform detailed histological characterization of the lesions. Specifically, macrophage infiltration, necrotic core formation, fibrosis, and fibrous cap thickness were not assessed. Finally, this study lacked in-depth mechanistic analyses. We did not evaluate inflammatory markers, oxidative stress parameters, or specific immune cell responses. Thus, the proposed role of lipid raft-associated signaling remains a hypothesis. Future studies are needed to elucidate the precise mechanisms underlying these observations.

5. Conclusions

In conclusion, exogenous ganglioside GM1 accelerates atherosclerotic lesion formation in apoE^{-/-} HFD mice. This pro-atherosclerotic effect contrasts with the previously reported anti-atherosclerotic properties of GM3. Our data show that GM1 treatment did not increase systemic cholesterol levels but significantly reduced TG levels. This indicates that the increase in lesion size is likely not a secondary effect of worsened systemic hyperlipidemia. Instead, exogenous GM1 may directly influence vascular

cells or the local plaque environment. However, the precise molecular mechanisms underlying this effect remain unclear. GM1 and its associated metabolic pathways represent important targets for understanding and potentially treating atherosclerosis.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

JH, JZ, and SF performed experiments, analyzed, and interpreted data. HZ analyzed and interpreted data, and revised the manuscript. JH prepared the draft. YC designed the research, analyzed and interpreted data, and revised the manuscript. MA analyzed and interpreted data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by Jiangxi University of Chinese Medicine Health Research Ethics Board (Reference No: JZLLSC2019-0255; approval date: Dec. 30, 2019). The study was carried out in accordance with the ARRIVE guidelines. The study was also performed in compliance with the national guidelines of China, including the Laboratory animal—Guideline for ethical review of animal welfare (GB/T 35892-2018).

Acknowledgment

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/FBL55490>.

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