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Theaflavin Attenuation of Atherosclerotic Inflammation via Regulation of Macrophage Pyroptosis Signaling Pathway

Wen Guo[1,a,*], Zihan Luo[1], Jing Xiang[1]

[1]Pharmacy Department, Affiliated Hospital of North Sichuan Medical College, Nanchong, 637000, China
[a]990907594@qq.com
[*]Corresponding author

Abstract: *Cell pyroptosis, a pro-inflammatory programmed cell death, plays a critical role in atherosclerosis (As) pathogenesis. Our previous studies have shown that theaflavin (TF), a polyphenolic compound, exhibits antioxidant and anti-inflammatory properties and can alleviate the progression of As. However, its impact on macrophage pyroptosis in As remains unexplored. Here, we investigated the effect of TF on pyroptosis in macrophages stimulated by oxidized low-density lipoprotein (ox-LDL). Our results demonstrated that TF significantly inhibited pyroptosis by suppressing the activation of caspase-1, reducing the cleavage of Gasdermin D (GSDMD), and downregulating the expression of NLRP3, interleukin-1β (IL-1β), and interleukin-1α (IL-1α). Additionally, TF decreased the production of reactive oxygen species (ROS), indicating its antioxidant role in mitigating pyroptosis. To verify whether the inhibitory effect of TF on pyroptosis is mediated by reducing ROS, we conducted experiments using N-acetylcysteine (NAC), a specific ROS inhibitor. We set up five groups: control group, ox-LDL group, ox-LDL + TF group, ox-LDL + NAC group, and ox-LDL + TF + NAC group. RT-qPCR detection revealed that the mRNA levels of pyroptosis-related genes in the ox-LDL + NAC group were significantly reduced, and the reduction was more pronounced in the ox-LDL + TF + NAC group, showing a synergistic effect between TF and NAC. These findings highlight that TF holds promise as a therapeutic agent for As by targeting oxidative stress and pyroptosis pathways.*

Keywords: *Pyroptosis, Atherosclerosis, Theaflavin*

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, accounting for approximately 17.9 million deaths annually, with atherosclerosis (As) as the primary pathological basis for most CVDs. Their causes are complex, and different pathological mechanisms can trigger cardiovascular diseases[1], including myocardial infarction and stroke. It is a multi-stage process involving endothelial dysfunction, lipid accumulation, immune cell infiltration, and chronic inflammation, where macrophages play a central role in lesion initiation and progression[2]. Atherosclerosis (atherosclemsis, As) is a common pathological basis for the occurrence and development of cardiovascular diseases[3]. The formation of atherosclerosis is related to long-term ischemia and hypoxia of blood vessels. When the lesion site is continuously ischemic and hypoxic, the imbalance of reactive oxygen species (ROS) and antioxidants will occur, resulting in oxidative stress, which will lead to inflammatory responses[4]. The inflammatory reactions further intensify, and cells die. Cell death plays an important role in the pathogenic mechanism of atherosclerosis. There are various ways of cell death, and pyroptosis is one of them. emerging evidence has identified pyroptosis, a pro-inflammatory form of programmed cell death, as a key driver of atherosclerotic plaque instability and disease progression[5].As your paper will be an important component in the journal, we highly recommend that all the authors follow this guideline to adjust the format of your paper so as to promise the highest reading experience.

Pyroptosis is morphologically and mechanistically distinct from other forms of cell death, such as apoptosis and necrosis. It is characterized by the activation of inflammasomes—multimeric protein complexes that sense cellular stress or pathogenic stimuli. Among inflammasomes, the NLRP3 (NOD-like receptor pyrin domain-containing 3) inflammasome is the most extensively studied in the context of As[6]. Upon activation by stimuli such as oxidized low-density lipoprotein (ox-LDL), cholesterol

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crystals, or reactive oxygen species (ROS), the NLRP3 inflammasome recruits and activates procaspase-1, which is then cleaved into its active form, cleaved caspase-1 (C-Caspase1). Activated caspase-1 further cleaves gasdermin D (GSDMD), a member of the gasdermin protein family, into its N-terminal (GSDMD-N) and C-terminal (GSDMD-C) fragments[7]. GSDMD-N oligomerizes to form pores in the cell membrane, leading to cell swelling, membrane rupture, and the release of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and interleukin-18 (IL-18), thereby amplifying local inflammatory responses in atherosclerotic lesions[8].

Oxidative stress, defined as an imbalance between the production of ROS and the cell's antioxidant defense capacity, is tightly intertwined with pyroptosis in As. ROS—including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH)—are primarily generated in mitochondria during oxidative phosphorylation[9, 10]. In macrophages, ox-LDL stimulation induces excessive ROS production, which not only damages cellular components such as lipids, proteins, and DNA but also acts as a critical upstream activator of the NLRP3 inflammasome. ROS-mediated oxidation of GSDMD further promotes its cleavage by caspase-1, creating a vicious cycle that accelerates macrophage pyroptosis and atherosclerotic lesion development[11]. Thus, targeting the ROS-pyroptosis axis has emerged as a promising therapeutic strategy for As.

Theaflavins (TFs) are a class of naturally occurring polyphenolic compounds unique to black tea, formed by the oxidation and condensation of catechins during tea fermentation. TFs are divided into several subtypes, including theaflavin (TF), theaflavin-3-gallate (TF-3-G), theaflavin-3'-gallate (TF-3'-G), and theaflavin-3,3'-digallate (TF-3,3'-DG), with TF being the most abundant and well-studied[12]. Accumulating evidence has demonstrated that TFs exhibit a broad spectrum of biological activities, including antioxidant, anti-inflammatory, anti-tumor, and lipid-lowering effects, making them potential candidates for the prevention and treatment of metabolic and inflammatory diseases[13]. Previous studies have shown that TFs can alleviate As by reducing endothelial dysfunction, inhibiting foam cell formation, and suppressing smooth muscle cell proliferation. For example, Zeng et al. reported that TF alleviates oxidative injury and As progression by activating microRNA-24-mediated Nrf2/HO-1 signaling, highlighting its antioxidative properties[14]. However, the specific role of TFs in regulating macrophage pyroptosis, particularly through the ROS-caspase-1-GSDMD pathway, remains poorly understood and requires systematic investigation.

In the present study, we aimed to explore the effect of TF on ox-LDL-induced macrophage pyroptosis and to elucidate its underlying molecular mechanisms, with a focus on the ROS-caspase-1-GSDMD signaling axis. Meanwhile, by setting up control groups containing N-acetylcysteine (NAC) (control group, ox-LDL group, ox-LDL + TF group, ox-LDL + NAC group, and ox-LDL + TF + NAC group), we intend to verify whether TF inhibits pyroptosis by reducing ROS and whether there is a synergistic effect between TF and NAC. We hypothesized that TF attenuates atherosclerotic inflammation by suppressing ROS-mediated macrophage pyroptosis, thereby providing experimental evidence for the clinical application of TF in As treatment. This study will not only expand our understanding of the anti-As mechanisms of TF but also contribute to the development of novel therapeutic strategies targeting pyroptosis for cardiovascular diseases.

2. Materials and Methods

2.1 Cell Culture and Treatment

Ana-1 macrophages (a mouse macrophage cell line) were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in RPMI 1640 medium (Gibco, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, USA) and 1% penicillin-streptomycin (Gibco, USA) at 37°C in a humidified incubator with 5% CO_2 and 1% O_2 (hypoxic conditions to mimic the atherosclerotic microenvironment).For dose-response experiments: Ana-1 macrophages were seeded in 6-well plates at a density of 5×10^5 cells/well. After 24 hours of adhesion, cells were divided into 4 groups:Control group: Cells were incubated with normal medium. It is advisable to keep all the given values. ox-LDL group: Cells were treated with 100 μg/mL ox-LDL (Yiyuan Biotechnology, Guangzhou, China).ox-LDL + 30 μM TF group: Cells were treated with 100 μg/mL ox-LDL + 30 μM TF (Sigma-Aldrich, USA).ox-LDL + 60 μM TF group: Cells were treated with 100 μg/mL ox-LDL + 60 μM TF.ox-LDL + 120 μM TF group: Cells were treated with 100 μg/mL ox-LDL + 120 μM TF.All groups were incubated under hypoxic conditions for 24 hours, after which cells were collected for RNA extraction and real-time quantitative PCR (RT-qPCR) analysis.

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2.2 ROS Detection

Ana-1 macrophages were added to 100 μg/mL oxidized low-density lipoprotein (ox-LDL) and divided into two groups. One group was treated with 60μM theaflavin, while the other served as the control. Both groups were co-incubated in a hypoxic incubator for 24 hours. The cells were collected and incubated with 10 μM DCFH-DA (Beyotime) for 30 minutes at 37°C in the dark. After resuspending in PBS, the fluorescence intensity was detected using a flow cytometer (BD FACSCalibur) at Ex/Em = 488/525 nm, and the data were analyzed with FlowJo.

2.3 Pyroptosis-Related Protein Analysis

Ana-1 macrophages were divided into two groups after being added with 100 μg/mL oxidized low-density lipoprotein (ox-LDL). One group was treated with 60 μM theaflavin, while the other served as the control. Proteins were extracted. The primary antibodies used were GSDMD (C#: ab219800) from Abcam, Caspase-1 (C#: 14F468) from NOVOS, cleaved caspase-1 (1:800, Abcam #ab179515), GSDMD-NT (1:1000, Affinity #AF4012), and Tubulin (Proteintech). The secondary antibody was HRP-labeled goat anti-rabbit/mouse IgG (1:5000, Proteintech). The bands were visualized using ECL and the gray values were quantified by ImageJ.

2.4 Real time Quantitative PCR (RT-qPCR)

Ana-1 macrophages were divided into 4 groups:Control group: Cells incubated with normal medium.ox-LDL group: Cells treated with 100 μg/mL ox-LDL; ox-LDL + TF group: Cells treated with 100 μg/mL ox-LDL + 60 μM TF; ox-LDL + NAC group: Cells treated with 100 μg/mL ox-LDL + 5 mM NAC (a specific ROS inhibitor); ox-LDL + TF + NAC group: Cells treated with 100 μg/mL ox-LDL + 60 μM TF + 5 mM NAC. All groups were incubated in a hypoxic incubator for 24 hours. After treatment, mRNA levels of IL-1β and NLRP3 were detected by RT-qPCR.

3. Results

3.1 TF Inhibits Pyroptosis-Related Inflammation in a Dose-Dependent Manner

To investigate the effect of TF on pyroptosis-related gene expression in ox-LDL-stimulated macrophages, we detected the mRNA levels of caspase-1, GSDMD, NLRP3, IL-1β, IL-1α, and IL-18 using RT-qPCR.Compared with the control group, the ox-LDL group showed significantly increased mRNA levels of all detected genes ($P < 0.05$), indicating that ox-LDL stimulation induces pyroptosis-related inflammation in Ana-1 macrophages. TF treatment dose-dependently reduced the mRNA expression of these genes: At 30μM, TF significantly decreased the mRNA levels of caspase-1, IL-1β, and IL-1α ($P < 0.05$), but had no significant effect on GSDMD, NLRP3, or IL-18 ($P > 0.05$). At 60 μM, TF significantly reduced the mRNA levels of all genes ($P < 0.01$), with a more pronounced inhibitory effect than the 30 μM group.At 120μM, TF exerted the strongest inhibitory effect, with mRNA levels of all genes being significantly lower than those in the 60 μM group ($P < 0.01$; Fig. 1).These results suggest that TF inhibits pyroptosis-related inflammation in ox-LDL-stimulated macrophages in a dose-dependent manner, with 60 μM and 120 μM showing more significant effects. Therefore, 60 μM was selected as the optimal concentration for subsequent experiments.

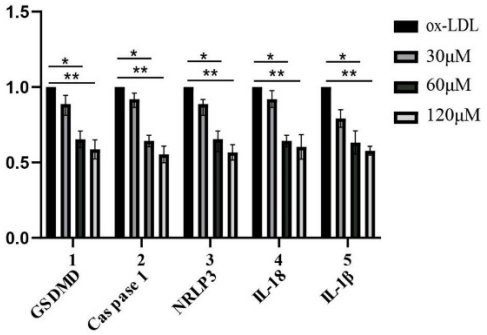

Fig.1: The expression of pyroptosis-related factors in macrophages after treatment with different concentrations of TF.

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Ana-1 macrophages were treated with ox-LDL alone or in combination with 30 μM, 60 μM, or 120 μM TF for 24 hours. RT-qPCR was used to detect the mRNA levels of GSDMD, caspase-1, NLRP3, IL-18, and IL-1β. Data are expressed as the mean ± SD (n=3). *P < 0.05, **P < 0.01 vs. ox-LDL group.

3.2 TF Suppresses Pyroptosis Protein Activation

To further explore the effect of TF on pyroptosis, we analyzed the protein levels of GSDMD, caspase-1, GSDMD-N, and C-Caspase1 using Western blot.As shown in Fig. 2A and 2B, the total protein levels of GSDMD and caspase-1 in the ox-LDL + TF group were not significantly different from those in the ox-LDL group (P > 0.05). However, TF treatment significantly reduced the expression of the active forms of these proteins: the levels of GSDMD-N and C-Caspase1 were decreased by 42.3% and 38.7%, respectively, compared with the ox-LDL group (both P < 0.01). These results confirm that TF inhibits macrophage pyroptosis by suppressing the activation of caspase-1 and the cleavage of GSDMD, rather than altering the total expression of these proteins.

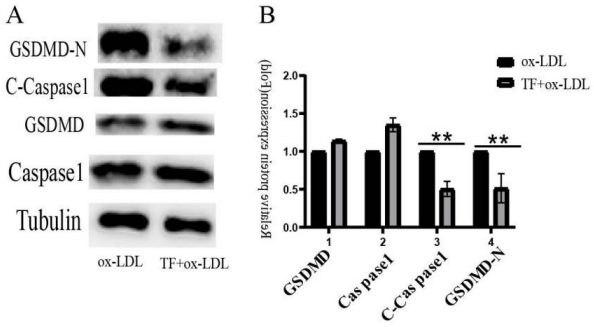

Fig.2: Protein expression of pyroptosis-related genes.

(A) Representative Western blot bands of GSDMD, caspase-1, GSDMD-N, C-Caspase1, and Tubulin in the ox-LDL group and ox-LDL + TF group. (B) Statistical analysis of relative protein expression levels, normalized to Tubulin. Data are expressed as the mean ± SD (n=3). **P < 0.01 vs. ox-LDL group.

3.3 Theaflavin reduces ox-LDL-induced ROS production in macrophages

To investigate whether TF modulates oxidative stress in ox-LDL-stimulated macrophages, we detected intracellular ROS levels using the DCFH-DA fluorescent probe and flow cytometry.Flow cytometry results showed that ox-LDL treatment significantly increased ROS levels, with the mean fluorescence intensity (MFI) being 2.3-fold higher than that in the control group (P < 0.01). Pretreatment with 60 μM TF significantly reduced ox-LDL-induced ROS production, with the MFI decreasing by 45.6% compared with the ox-LDL group (P < 0.01; Fig. 3), indicating that TF effectively alleviates oxidative stress in macrophages under atherosclerotic conditions.

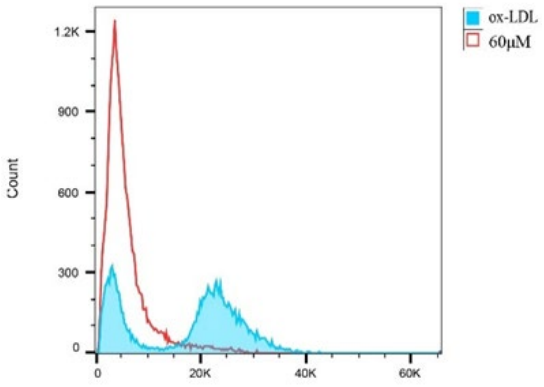

Fig.3: ROS levels measured by flow cytometry.

Flow cytometry was used to analyze reactive oxygen species (ROS)-positive cells in macrophages. Red and blue histograms represent the ox-LDL group and ox-LDL + 60 μM TF group, respectively. The y-axis indicates cell count, and the x-axis indicates fluorescence intensity (DCF), reflecting ROS levels. Data are representative of three independent experiments.

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3.4 The reduction of ROS inhibited pyroptosis of macrophages

To confirm whether the inhibitory effect of TF on pyroptosis is mediated by reducing ROS, we used NAC (a specific ROS inhibitor) and detected the mRNA levels of pyroptosis-related genes in five groups (As shown in Fig. 4): control, ox-LDL, ox-LDL + TF, ox-LDL + NAC, and ox-LDL + TF + NAC. RT-qPCR results showed that:Compared with the ox-LDL group, the mRNA levels of caspase-1, GSDMD, NLRP3, and IL-1β in the ox-LDL + NAC groups were significantly reduced (all $P < 0.05$), with a similar inhibitory effect to the ox-LDL + TF group ($P > 0.05$ between the two groups). The ox-LDL + TF + NAC group exhibited the lowest mRNA levels of all detected genes, with reductions of 52.1% (caspase-1), 49.8% (GSDMD), 56.3% (NLRP3), and 54.5% (IL-1β) compared with the ox-LDL group (all $P < 0.01$), indicating a synergistic effect of TF and NAC in suppressing pyroptosis-related gene expression.

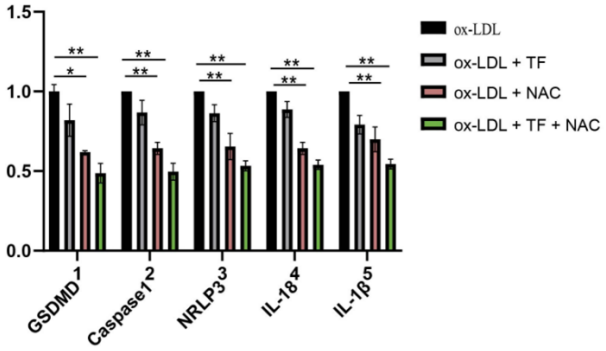

Fig.4: The changes in pro-apoptotic mRNA in macrophages were observed under the treatments of ox-LDL group, ox-LDL + TF group, ox-LDL + NAC group, and ox-LDL + TF + NAC group.

Control group: Cells incubated with normal medium.ox-LDL group: Cells treated with 100 μg/mL ox-LDL; ox-LDL + TF group: Cells treated with 100 μg/mL ox-LDL + 60 μM TF; ox-LDL + NAC group: Cells treated with 100 μg/mL ox-LDL + 5 mM NAC (a specific ROS inhibitor); ox-LDL + TF + NAC group: Cells treated with 100 μg/mL ox-LDL + 60 μM TF + 5 mM NAC. The results were expressed as mean ± standard deviation, n=3, *P<0.05, **P<0.001, vs ox-LDL.

4. Discussion

Atherosclerosis has progressively emerged as one of the leading causes of mortality in cardiovascular diseases, characterized by a complex pathogenesis involving multiple cellular and molecular mechanisms[15]. In this study, we have systematically investigated how theaflavin, a bioactive polyphenol derived from tea, ameliorates atherosclerotic inflammation through its regulatory effects on macrophage oxidative stress and pyroptosis signaling pathways. Macrophages play a pivotal role in atherosclerotic plaque development, where their dysfunction contributes significantly to disease progression through oxidative stress and inflammatory responses.

Macrophages serve as central immune cells in the initiation and progression of atherosclerosis (AS), actively participating in all stages from early lipid deposition to advanced plaque rupture[16]. Circulating monocytes migrate into the vascular intima under the influence of chemokines, such as monocyte chemoattractant protein-1 (MCP-1), where they differentiate into macrophages[17]. These macrophages internalize oxidized low-density lipoprotein (ox-LDL) via scavenger receptors, including SR-A1 and CD36, leading to intracellular cholesterol accumulation and their transformation into "foam cells," which are hallmark components of atherosclerotic lesions[18]. During this process, the activation of NLRP3 and the production of reactive oxygen species (ROS) are triggered, thereby amplifying inflammatory responses and accelerating the progression of pyroptosis. Targeting GSDMD or Caspase-1 (such as the flavonoid theaflavin) may reduce the production of ROS to inhibit the formation of atherosclerosis.

Theaflavin exhibits a remarkable spectrum of biological activities, including potent antioxidant properties, cardiovascular protection, anti-inflammatory and antimicrobial effects, as well as metabolic regulation[19]. Accumulating evidence demonstrates its efficacy in scavenging free radicals and suppressing oxidative stress. Our experimental findings reveal that theaflavin exerts dose-dependent inhibitory effects on key pyroptosis-related markers in macrophages, including Caspase-1, GSDMD, NLRP3, and inflammatory cytokines IL-1β and IL-1α. Importantly, we observed that theaflavin significantly suppresses ox-LDL-induced activation of the NLRP3 inflammasome, cleavage of Caspase-

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1 (C-Caspase1), and expression of GSDMD-N terminal domain in macrophages, thereby effectively attenuating macrophage pyroptosis. These results provide novel molecular insights into the anti-atherosclerotic mechanisms of theaflavin, particularly through its modulation of macrophage inflammatory responses.

Oxidative stress, mediated by excessive ROS production, is a well-established trigger of atherosclerotic inflammation. ROS not only causes lipid peroxidation and endothelial damage but also acts as a critical signaling molecule to activate the NLRP3 inflammasome and promote GSDMD oxidation, thereby accelerating macrophage pyroptosis[20]. Our study demonstrates that TF significantly reduces ox-LDL-induced ROS accumulation in macrophages, which is consistent with prior reports that TF scavenges free radicals and enhances antioxidant defenses via the Nrf2/HO-1 pathway.

To verify whether ROS reduction contributes to TF's anti-pyroptotic effect, we used NAC, a specific ROS inhibitor. The results showed that NAC mimics TF's ability to downregulate pyroptosis-related genes (caspase-1, GSDMD, NLRP3, and IL-1β), confirming that ROS is a downstream mediator of TF's inhibitory effect on pyroptosis. Furthermore, co-treatment with TF and NAC exerted a synergistic effect, with significantly lower expression of pyroptosis markers compared to either treatment alone. This suggests that TF and NAC may act through complementary mechanisms to reduce ROS levels—for example, TF may enhance antioxidant enzyme activity, while NAC directly scavenges ROS—leading to more robust suppression of the ROS-pyroptosis axis.

The inhibition of ROS generation by theaflavin in macrophages represents a crucial mechanism underlying its anti-inflammatory effects. As ROS serves as a fundamental trigger for NLRP3 inflammasome activation in macrophages, our demonstration that theaflavin reduces intracellular ROS levels and consequently inhibits pyroptosis signaling pathways in these immune cells strongly supports its potential therapeutic value in cardiovascular diseases. This finding is consistent with previous reports of theaflavin's antioxidant properties while extending our understanding to its specific effects on macrophage biology.

Furthermore, our study highlights theaflavin's significant impact on macrophage-derived inflammatory mediators. The compound's inhibition of pro-inflammatory cytokine release (particularly IL-1β and IL-1α) from macrophages likely constitutes another important mechanism for alleviating atherosclerotic inflammation. These cytokines, predominantly secreted by activated macrophages, play pivotal roles in all stages of atherosclerotic plaque formation and progression. By modulating macrophage cytokine production, theaflavin may effectively interrupt the vicious cycle of inflammation that drives atherosclerosis development.

The present findings have important clinical implications for as treatment. TF is a natural polyphenol with excellent safety profiles, and its abundance in black tea makes it a readily accessible candidate for dietary intervention[10]. Our results suggest that TF could be developed as a therapeutic agent to target macrophage pyroptosis and oxidative stress in As, particularly in patients with high levels of ox-LDL or systemic inflammation. Moreover, the synergistic effect of TF and NAC provides a rationale for combining antioxidants to enhance anti-atherosclerotic efficacy. However, several limitations should be acknowledged. First, our experiments were conducted in vitro using Ana-1 macrophages, and in vivo studies are needed to validate whether TF inhibits pyroptosis in atherosclerotic plaques of animal models (e.g., ApoE$^{-/-}$ mice) and whether it reduces plaque size or instability. Second, we focused on the ROS-caspase-1-GSDMD pathway, but TF may modulate other pyroptosis-related molecules (e.g., gasdermin E) or signaling pathways (e.g., NF-κB) that contribute to As. Third, the pharmacokinetic properties of TF—such as its bioavailability and tissue distribution—need to be optimized for clinical translation, as polyphenols are often rapidly metabolized[10].our study provides compelling evidence that theaflavin mitigates atherosclerotic inflammation through its multifaceted actions on macrophages, including suppression of oxidative stress and inhibition of pyroptosis signaling pathways. These findings significantly advance our understanding of theaflavin's mechanisms of action and strengthen its potential as a promising cardiovascular protective agent. Future research should focus on translating these mechanistic insights into preclinical and clinical applications, with particular attention to optimizing theaflavin's bioavailability and therapeutic efficacy in macrophage-rich atherosclerotic lesions.

5. Conclusion

Theaflavin (TF) alleviates atherosclerotic inflammation by regulating macrophage pyroptosis through the caspase-1 signaling pathway and oxidative stress pathways. Specifically, TF inhibits the activation of caspase-1, reduces the cleavage of GSDMD, and downregulates the expression of NLRP3, IL-1β, and

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IL-1α, thereby suppressing pyroptosis. It also reduces ROS production, exerting an antioxidant effect in mitigating pyroptosis. Furthermore, experiments using N-acetylcysteine (NAC) confirm that the inhibitory effect of TF on pyroptosis is mediated by reducing ROS, and there is a synergistic effect between TF and NAC in inhibiting the expression of pyroptosis-related genes, which further enhances the therapeutic potential of TF in targeting the ROS-pyroptosis axis. These findings indicate that TF holds promise as a therapeutic strategy for atherosclerosis-related inflammation, providing a new direction for the prevention and treatment of cardiovascular diseases.

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