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ORIGINAL ARTICLE

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Fucoxanthin mitigates inflammation and angiogenesis in rheumatoid arthritis via regulation of the PPAR-γ/CTGF pathway

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Abstract
Background: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that causes joint pain and significantly impairs patients' quality of life. Fucoxanthin, a naturally occurring carotenoid found in seaweeds and diatoms, has been reported to exert various therapeutic effects in multiple pathological conditions. However, its regulatory role in the pathogenesis of RA remains largely undefined.
Methods: Cell viability was assessed using the cell counting kit-8 (CCK-8) assay, while cell migration and invasion were evaluated through the wound healing and Transwell assays, respectively. Angiogenic potential was determined by the tube formation assay. The levels of pro-inflammatory cytokines, including interleukin (IL)-6, IL-1β, and IL-8, were measured using enzyme-linked-immunosorbent serologic assay. Intracellular reactive oxygen species (ROS) levels were analyzed via DCFH-DA staining, and protein expression was evaluated by Western blot analysis.
Results: Fucoxanthin significantly suppressed tumor necrosis factor-α (TNF-α)-induced proliferation of MH7A synovial cells. Additionally, TNF-α stimulation enhanced cell migration and invasion, whereas these effects were reversed with fucoxanthin treatment. TNF-α also promoted angiogenesis, as evidenced by an increased number of tube formations, which were markedly reduced by fucoxanthin in a dose-dependent manner (control; TNF-α; TNF-α + fucoxanthin [2 μM]; and TNF-α + fucoxanthin [4 μM], with respective values of 1.33 ± 0.58; 26 ± 3.61; 17 ± 2.65; and 8.33 ± 1.53; $P < 0.001$). Moreover, fucoxanthin alleviated TNF-α-induced inflammatory cytokine release and oxidative stress. Mechanistically, fucoxanthin was found to regulate the PPAR-γ/CTGF signaling pathway.
Conclusion: Fucoxanthin may attenuate inflammation and angiogenesis in RA by modulating the PPAR-γ/CTGF pathway, suggesting its potential as a therapeutic agent for managing RA.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease primarily affecting synovial joints.[1] Its incidence is influenced by environmental factors; for instance, the prevalence of RA is higher in plateau regions, compared to plain areas, which may be attributed to lower temperatures, dryness, and hypoxic conditions characteristic of high-altitude environments.[2] A hallmark of RA is persistent synovial inflammation, which leads to progressive cartilage erosion, synovial hyperplasia, and joint deformity.[3,4] Therefore, the identification of effective therapeutic agents to slow down or halt the progression of the disease remains an urgent clinical need.

Fucoxanthin (FX) is an oxygenated carotenoid discovered predominantly in brown algae.[5] Increasing evidence suggests that fucoxanthin exerts protective effects across various pathological conditions. For example, it was shown to activate the nuclear factor erythroid 2-related factor 2–signal transducer and activator of transcription 3 (Nrf2/STAT3) signaling pathway to inhibit ferroptosis, thereby alleviating lipopolysaccharide-induced acute lung injury.[6] It also modulates the adenosine monophosphate-activated protein kinase–glycogen synthase kinase 3-Nrf2 (AMPK/GSK-3β/Nrf2) axis to attenuate myocardial ischemia/reperfusion injury,[7] and has demonstrated anti-inflammatory properties in experimental models of colitis induced by dextran sulfate sodium.[8] Furthermore, fucoxanthin is reported to inhibit nuclear factor kappa B (NF-κB) nuclear translocation, thereby reducing Propionibacterium acnes-induced ear inflammation.[9] In the musculoskeletal system, fucoxanthin is found to regulate the Nrf2 pathway to suppress osteoclastogenesis,[10] and microalgae-derived fucoxanthin is shown to influence the Janus kinase–STAT (JAK/STAT) signaling pathway to attenuate RA progression.[11] Despite these promising findings, the precise molecular mechanisms underlying fucoxanthin's effect in RA, particularly in relation to specific signaling pathways, remain insufficiently characterized.

Recent studies have highlighted the involvement of the peroxisome proliferator-activated receptor gamma (PPAR-γ)/connective tissue growth factor (CTGF) signaling pathway in modulating inflammation and cellular apoptosis in RA. For instance, Shentong Zhuyu decoction has been shown to inhibit inflammatory responses and promote apoptosis by targeting the mitogen-activated protein kinase (MAPK) p38/PPAR-γ/CTGF pathway in RA models.[12] However, whether fucoxanthin exerts similar regulatory effects on this pathway during RA progression has not yet been clarified.

Therefore, the present study aimed to explore the role of fucoxanthin in RA and to elucidate its potential regulatory mechanisms, particularly through the PPAR-γ/CTGF signaling axis. The findings may provide new insights into the therapeutic utility of fucoxanthin for managing RA.

Materials and Methods

Cell lines and cell culture

Human fibroblast-like synoviocytes (MH7A) and human umbilical vein endothelial cells (HUVECs) were obtained from the American Type Culture Collection (ATCC, USA). Both cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco, USA) supplemented with 10% fetal bovine serum (FBS) in a humidified incubator maintained at 37°C with 5% CO_2. All cell lines were authenticated by short tandem repeat (STR) profiling and confirmed to be free of mycoplasma contamination.

To establish an *in vitro* model of RA, MH7A cells were treated with tumor necrosis factor-alpha (TNF-α) at a concentration of 10 μg/mL for 24 h, as described previously.[13,14]

Morusin was prepared in a series of concentrations (0.5, 1, 2, 4, 8, and 16 μg/mL; Shanghai Selleck Chemicals Co. Ltd., Shanghai, China) for subsequent assays.

CCK-8 assay

MH7A cells were seeded into 96-well plates at appropriate densities. After treatment, 10 μL of cell counting kit-8 (CCK-8) reagent (Dojindo Laboratories, Kumamoto, Japan) was added to each well and incubated for 2 h. Absorbance was measured at 450 nm using a microplate reader (Thermo Fisher Scientific, MA, USA) to evaluate cell viability.

Wound healing assay

MH7A cells were plated into 6-well plates and allowed to reach confluence. A sterile pipette tip was used to create a linear scratch in cell monolayer. After 24 h of incubation, wound closure was imaged using a phase-contrast microscope (Olympus Corporation, Tokyo, Japan) to assess cell migration.

Transwell assay (cell invasion)

Cell invasion was assessed using Transwell chambers with 8-μm pore polycarbonate membranes (Corning, NY, USA) coated with Matrigel (BD Biosciences, NJ, USA). MH7A cells suspended in 200 μL of serum-free medium were seeded in upper chambers. Lower chambers contained 600 μL of medium supplemented with 20% FBS as a chemoattractant. After 48 h, cells that had invaded through the membrane were fixed with 4% paraformaldehyde, stained with 0.1% crystal violet, and imaged using a microscope (Olympus Optical Co).

Tube formation assay

HUVECs were seeded into 24-well plates pre-coated with polymerized matrigel (BD Biosciences, MA, USA) and incubated with 200 μL of conditioned medium collected from MH7A cells. After 12 h, tube-like structures were visualized and captured using a light microscope (Olympus Optical Co). Each experiment was performed in triplicate.

Enzyme-linked immunosorbent serologic assay (ELISA)

MH7A cells (5×10^5 cells/well) were seeded into 12-well plates and incubated for 24 h. Culture supernatants were

harvested and assayed for interleukin (IL)-1β (ab214025), IL-6 (ab178013), and IL-8 (ab214030) using commercial ELISA kits (Abcam, Shanghai, China) by following the manufacturers' protocol.

2',7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) staining

Intracellular ROS levels were measured using a DCFH-DA fluorescence assay kit (E004-1-1, Nanjing Jiancheng Bioengineering Institute, China). MH7A cells were incubated with DCFH-DA, and fluorescent signals were detected using a fluorescence microscope (Olympus, Tokyo, Japan).

Western blot analysis

Total protein concentration was determined using the bicinchoninic acid (BCA) assay kit (Beyotime Institute of Biotechnology, Shanghai, China). Equal quantity of proteins extracted from MH7A cells was separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and subsequently transferred onto polyvinylidene fluoride (PVDF) membranes (Beyotime). After blocking with 5% non-fat milk, the membranes were incubated overnight at 4°C with the following primary antibodies: anti-PPAR-γ (dilution 1:1000; ab178860, Abcam); anti-CTGF (dilution 1:500; ab318148; Abcam), and anti-β-actin (dilution 1:1000; ab8226; Abcam). Then, after washing, the membranes were incubated for 2 h at room temperature with a horseradish peroxidase (HRP)-conjugated secondary antibody (dilution 1:2000; ab7090; Abcam). Protein bands were visualized using a chemiluminescence detection system (Thermo Fisher Scientific Inc.) and quantified using the ImageJ software.

Statistical analysis

All data were presented as mean ± standard deviation (SD). The normality of the data distribution was assessed using the Shapiro-Wilk test. Statistical analyses were performed using the GraphPad Prism 9 software (GraphPad Software, USA). Each experiment was conducted in triplicate. One-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test was used to compare differences among multiple groups; $P < 0.05$ was considered statistically significant.

Results

Fucoxanthin inhibits TNF-a-induced proliferation of MH7A cells

The chemical structure of fucoxanthin is presented in Figure 1A. To assess its cytotoxicity, MH7A cell viability was examined following exposure to various concentrations of fucoxanthin. A dose-dependent decrease in viability was observed at higher concentrations (8 and 16 μM) of fucoxanthin, indicating a suppressive effect on cell proliferation (Figure 1B). Furthermore, TNF-α stimulation significantly reduced MH7A cell viability, consistent with an inflammatory phenotype. Notably, treatment with fucoxanthin at 2 μM or 4 μM effectively reversed this reduction, as evidenced by restored optical density (OD) values (Figure 1C). These findings suggest that fucoxanthin, at appropriate

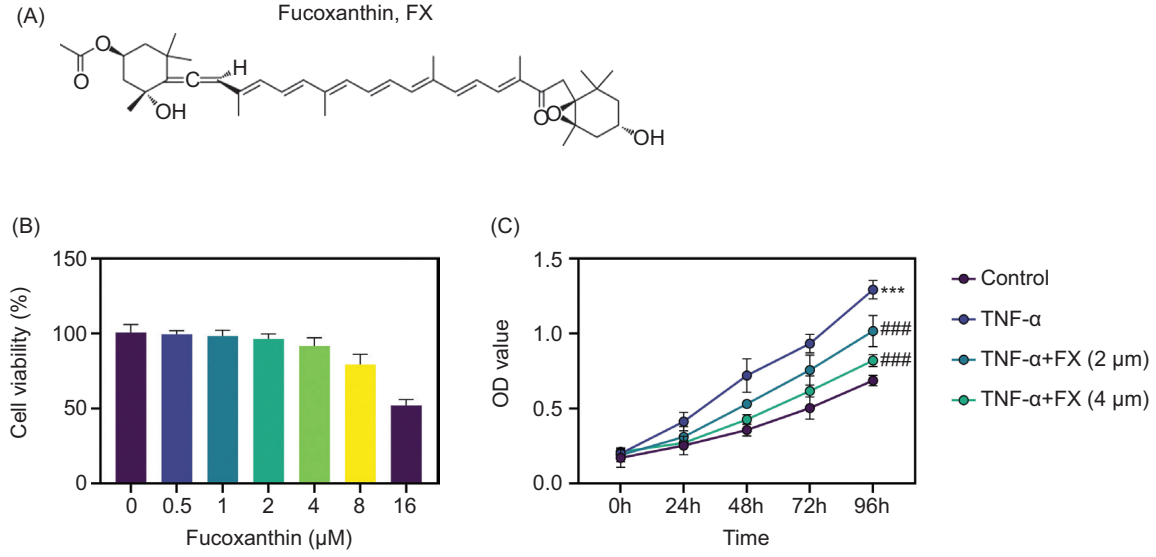

Figure 1 Fucoxanthin inhibits TNF-α-induced proliferation of MH7A cells. (A) Chemical structure of fucoxanthin; (B) MH7A cell viability following treatment with fucoxanthin at concentrations of 0, 0.5, 1, 2, 4, 8, and 16 μM was assessed using the CCK-8 assay; (C) cell viability was further evaluated by measuring OD values in the control, TNF-α, TNF-α + fucoxanthin (2 μM), and TNF-α + fucoxanthin (4 μM) groups; N = 3. $P < 0.01$, $^{*}P < 0.001$ vs. control group; $^{###}P < 0.001$ vs. TNF-α group.

concentrations, attenuates TNF-α-induced proliferative responses in MH7A cells without inducing cytotoxicity.

Fucoxanthin suppressed TNF-a-stimulated migration and invasion of MH7A cells

As shown in Figure 2A, TNF-α treatment markedly impaired cell migration, compared to the control group (control, TNF-α, TNF-α + FX [2 μM], and TNF-α + FX [4 μM], with respective values of 53.76 ± 3.62, 37.49 ± 5.20, 48.38 ± 2.13, and 53.03 ± 2.09; $P < 0.05$), whereas co-treatment with fucoxanthin at 2 μM or 4 μM restored migration to near-control levels. Similarly, TNF-α stimulation significantly enhanced the invasive capacity of MH7A cells, which was dose-dependently suppressed by fucoxanthin (control, TNF-α, TNF-α + FX [2 μM], TNF-α + FX [4 μM], with respective values of 45.33 ± 8.51, 180.7 ± 11.02, 108.3 ± 4.16, and 76.33 ± 7.77; $P < 0.001$) (Figure 2B). Together, these results demonstrate that fucoxanthin can effectively counteract TNF-α-induced migratory and invasive behaviors in MH7A cells.

Fucoxanthin attenuated TNF-a-induced angiogenesis

TNF-α stimulation markedly promoted endothelial tube formation, reflecting increased angiogenic potential. However, conditioned media derived from MH7A cells treated with fucoxanthin at 2 μM or 4 μM significantly inhibited this TNF-α-induced angiogenesis in a concentration-dependent manner (control, TNF-α, TNF-α + FX [2 μM], TNF-α + FX [4 μM], with respective alues of 1.33 ± 0.58, 26.00 ± 3.61, 17.00 ± 2.65, and 8.33 ± 1.53; $P < 0.001$) (Figure 3), indicating that fucoxanthin may impair the angiogenic signaling mediated by TNF-α-exposed MH7A cells.

Fucoxanthin mitigated TNF-a-induced inflammatory cytokine production and oxidative stress

TNF-α significantly elevated the secretion of IL-6, IL-1β, and IL-8, whereas fucoxanthin treatment at 2 μM or 4 μM markedly suppressed the levels of these pro-inflammatory cytokines (Figure 4A). Additionally, intracellular ROS accumulation was substantially increased following TNF-α exposure, reflecting oxidative stress; however, fucoxanthin significantly reduced ROS levels in a dose-dependent manner (control, TNF-α, TNF-α + FX [2 μM], and TNF-α + FX [4 μM], with respective values of 1.13 ± 0.38, 5.68 ± 0.60, 4.46 ± 0.46, and 2.23 ± 0.20; $P < 0.001$) (Figure 4B). These data confirmed that fucoxanthin effectively suppressed both inflammatory mediator release and oxidative stress triggered by TNF-α.

Fucoxanthin modulated the PPAR-γ/CTGF pathway

Following TNF-α stimulation, the expression of PPAR-γ was significantly downregulated, while CTGF expression

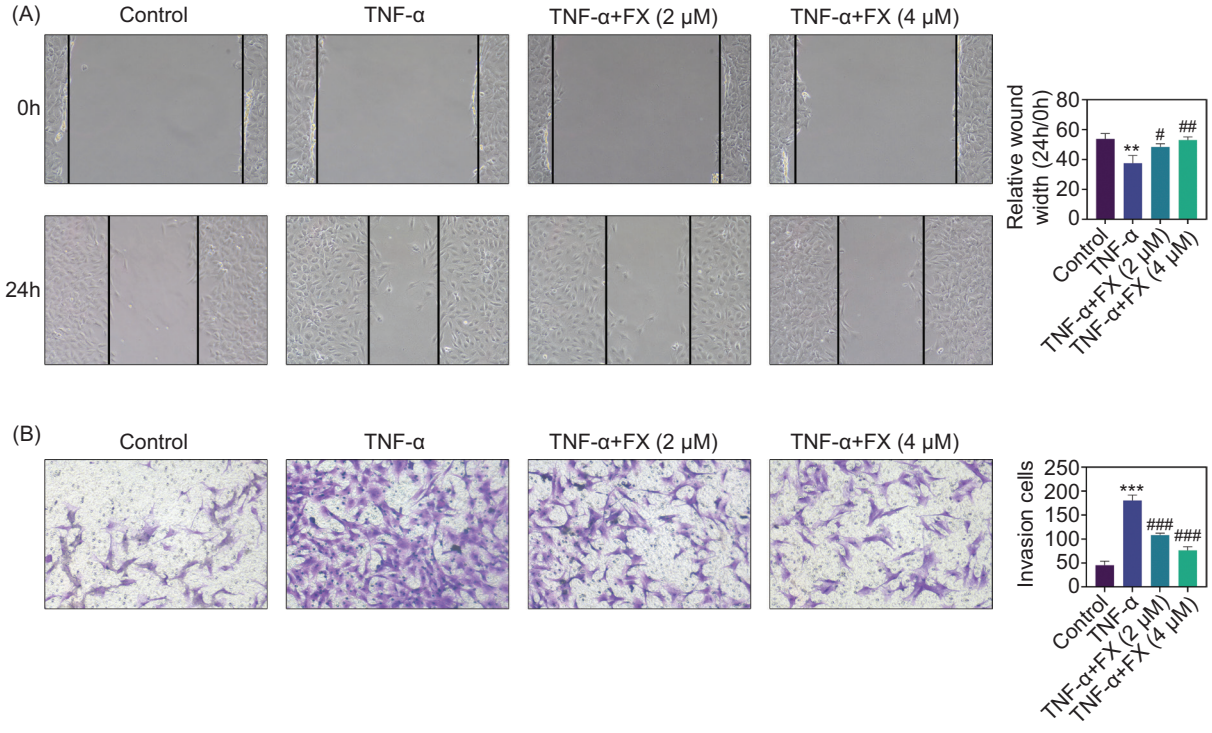

Figure 2 Fucoxanthin suppresses TNF-α-stimulated cell migration and invasion. MH7A cells were divided into control, TNF-α, TNF-α + fucoxanthin (2 μM), and TNF-α + fucoxanthin (4 μM) groups. (A) Cell migration was evaluated using a wound healing assay; (B) cell invasion was assessed using the matrigel-coated transwell assay; N = 3, $P < 0.01$, $^{*}P < 0.001$ vs. control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. TNF-α group.

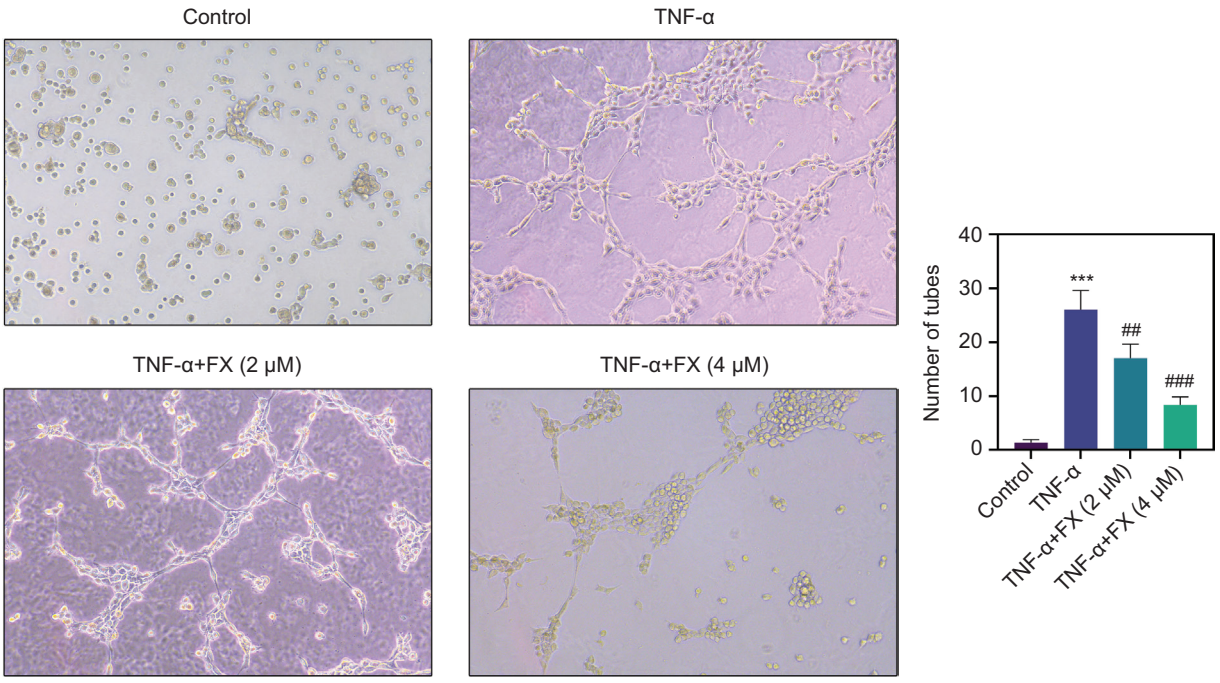

Figure 3 Fucoxanthin attenuates TNF-α-induced angiogenesis. HUVECs were cultured with conditioned media derived from MH7A cells in Control, TNF-α, TNF-α + fucoxanthin (2 μM), and TNF-α + fucoxanthin (4 μM) groups. Tube formation assays were used to assess angiogenic capacity; N = 3, $^{*}P < 0.001$ vs. control group; $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. TNF-α group.

was upregulated. However, co-treatment with fucoxanthin at 2 μM or 4 μM effectively reversed these alterations, restoring PPAR-γ levels and suppressing CTGF expression (Figure 5), thereby suggesting that fucoxanthin modulated the PPAR-γ/CTGF signaling pathway in MH7A cells.

Discussion

Fucoxanthin is studied for its beneficial effects in various pathological conditions.[6-11] However, its regulatory character in the progression of RA is not fully elucidated. In RA, fibroblast-like synoviocytes (RA-FLS) are known to exhibit tumor-like characteristics, including abnormal proliferation, migration, and invasion.[15] Excessive proliferation of RA-FLS contributes to synovial hyperplasia and joint destruction in affected patients.[16] In the present study, we demonstrated that fucoxanthin significantly suppressed TNF-α-induced proliferation of MH7A cells, a widely used RA-FLS model. Furthermore, the enhanced migratory and invasive capacities observed following TNF-α stimulation were markedly attenuated with fucoxanthin treatment, indicating its potential to inhibit pathological synoviocyte behavior under inflammatory conditions. Angiogenesis plays a central role in the pathophysiology of RA by supporting pannus formation and sustaining chronic inflammation. Recent studies have emphasized its therapeutic relevance, showing that anti-angiogenic agents, such as clematichinenoside AR (CAR)[17] and Huayu Tongbi formula effectively alleviated progression of the disease by targeting synovial vascularization.[18] Additionally, molecular regulators, such as miR-378, are implicated in promoting angiogenesis through modulation of endoplasmic reticulum stress in experimental RA models.[19] Consistent with these reports, our results revealed that TNF-α stimulation markedly promoted tube formation in HUVECs, suggesting elevated angiogenic potential. However, conditioned media from fucoxanthin-treated MH7A cells significantly suppressed this response, highlighting fucoxanthin's anti-angiogenic capacity in an RA-relevant context.

Inflammation and oxidative stress are closely intertwined and represent key drivers of RA pathology.[20,21] Numerous studies have explored agents capable of disrupting this pathological axis. For instance, tangeretin has been shown to attenuate both inflammation and oxidative stress in collagen-induced arthritis models,[22] and extracts of *Cassia fistula* fruit pulp have also demonstrated similar effects.[23] DUOX1 and gossypin are also identified as modulators of NF-κB signaling and oxidative injury in RA models, respectively.[24,25] In line with these findings, the present study showed that fucoxanthin significantly reduced TNF-α-induced secretion of pro-inflammatory cytokines (IL-6, IL-1β, and IL-8) and suppressed ROS accumulation in MH7A cells, suggesting its dual anti-inflammatory and antioxidative properties.

Among the molecular mechanisms underlying RA progression, PPAR-γ has emerged as a critical transcription factor with anti-inflammatory functions.[26] One of its downstream effectors, CTGF, is known to regulate fibrosis, angiogenesis, and tissue remodeling, and is implicated in RA-associated joint destruction.[27] Nozawa et al. indicated that CTGF can promote osteoclastogenesis to accelerate joint damage in RA patients,[28] and Ding et al. discovered that CTGF can facilitate the proliferation of

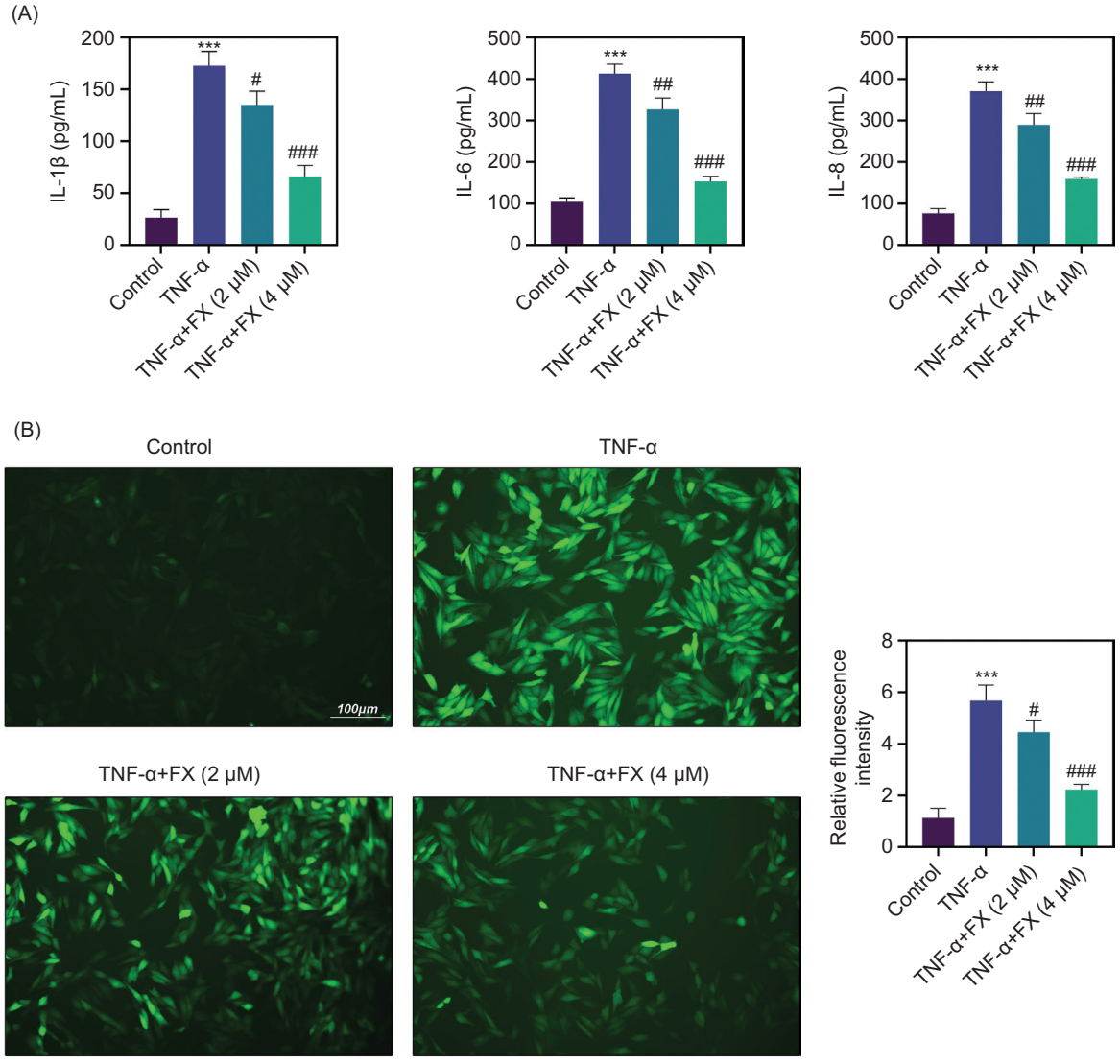

Figure 4 Fucoxanthin alleviates TNF-α-induced inflammation and oxidative stress. MH7A cells were grouped as control, TNF-α, TNF-α + fucoxanthin (2 μM), and TNF-α + fucoxanthin (4 μM). (A) Levels of IL-6, IL-1β, and IL-8 in culture supernatants were measured using ELISA; (B) intracellular ROS levels were assessed using DCFH-DA fluorescence staining; N = 3, $^{*}P < 0.001$ vs. control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. TNF-α group.

fibroblast-like synoviocytes to strengthen joint damage in RA.[29] Interestingly, traditional formulations, such as Shentong Zhuyu decoction, have been shown to inhibit RA progression by targeting the MAPK p38/PPAR-γ/CTGF axis.[12] However, regulatory effects of fucoxanthin on this pathway are not investigated. In this study, we observed that stimulation of TNF-α downregulated PPAR-γ expression while upregulating CTGF in MH7A cells. Notably, fucoxanthin treatment reversed these effects, suggesting that its protective functions may be mediated through modulation of PPAR-γ/CTGF signaling pathway.

Conclusion

This study is the first to demonstrate that fucoxanthin attenuates inflammation, migration, invasion, and angiogenesis in TNF-α-stimulated MH7A cells, potentially through regulation of PPAR-γ/CTGF axis. While these findings provide mechanistic insight into the anti-RA potential of fucoxanthin, several limitations must be acknowledged. These include the absence of *in vivo* validation, the exclusive use of an immortalized cell line, rather than primary human synoviocytes, and the need for further mechanistic exploration and preclinical evaluation. The future research should incorporate animal models, primary cells, and pathway-specific interventions to confirm and expand upon the current findings.

Ethics Approval

This article did not contain any studies with human participants or animals performed by any of the authors.

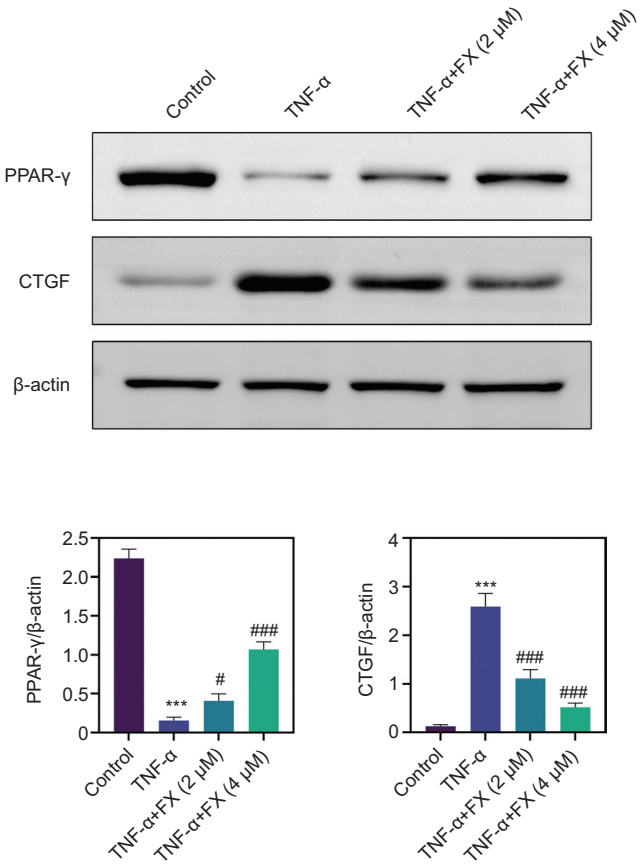

Figure 5 Fucoxanthin modulates the PPAR-γ/CTGF signaling pathway. MH7A cells were treated as indicated in the control, TNF-α, TNF-α + fucoxanthin (2 μM), and TNF-α + fucoxanthin (4 μM) groups. Protein expression levels of PPAR-γ and CTGF were determined by Western blot analysis; N = 3. $^{*}P < 0.001$ vs. control group; $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ vs. TNF-α group.

Data Availability

The authors declared that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

Author's Contribution

Ximing Zhao and Xingli Zhou designed the study and carried the same; Ximing Zhao, Xingli Zhou, and Famin Li supervised data collection, analyzed and interpreted the data, and prepared the manuscript for publication and reviewed its draft. All authors had read and approved the final manuscript.

Conflict of Interest

The authors stated that there was no conflict of interest to disclose.

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