



In vivo therapeutic effects of reactive oxygen species (ROS)-scavenging nanotherapeutics on dextran sulphate sodium-induced acute colitis model

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Abstract

Excess reactive oxygen species (ROS) and persistent oxidative stress can cause mucosal damage and epithelial dysfunction, accelerating inflammation and the development of inflammatory bowel diseases (IBD). Thus, ROS-scavenging and anti-inflammatory nanomaterials have emerged as promising strategies for treating IBD. Herein, we developed ROS-scavenging anti-inflammatory tannic acid (TA)-iron ion (Fe^{2+})-quercetin (QCT) (TFQ) nanocomplexes via a coordination-based self-assembly process, and evaluated their therapeutic effects on dextran sulphate sodium (DSS)-induced acute colitis mouse model. The prepared TFQ nanocomplexes exhibited good colloidal and storage stabilities under aqueous condition. In addition, they showed excellent free radical- and hydrogen peroxide (H_2O_2)-scavenging activities. Further, the cytocompatible TFQ nanocomplexes inhibited pro-inflammatory cytokines (i.e. IL-6 and IL-1 β), achieving remarkable anti-inflammatory effects against lipopolysaccharide (LPS)-treated macrophages and cytoprotective effects against H_2O_2 -treated macrophages. Moreover, systemically administered TFQ nanocomplexes alleviated disease symptoms, including colon shortening and inflammation, in a DSS-induced acute colitis mouse model. These findings suggested that the ROS-scavenging anti-inflammatory TFQ nanocomplexes are a promising therapeutic approach for IBD therapy.

Keywords Inflammatory bowel diseases · Reactive oxygen species scavenging · Anti-inflammation · Quercetin · Tannic acid · Coordination-based self-assembly

1 Introduction

Inflammatory bowel diseases (IBD) are chronic gastrointestinal disorders characterised by an abnormal immune response [1]. Although the pathogenesis of IBD is not yet fully understood, previous studies have suggested that many factors, including genetic susceptibility, commensal microbiota, infectious factors, immune system dysfunction and the external environment may contribute to IBD [2, 3]. Traditional clinical medications, such as aminosalicylates, glucocorticoids, immunomodulators, and biologics, can effectively alleviate IBD symptoms by relieving inflammation. However, not all patients exhibit satisfactory responses to medications, and severe adverse effects,

including hepatotoxicity, infections, and malignancies, are highly probable [3, 4]. Therefore, the development of novel therapeutic strategies for treating IBD is urgently required.

Recent studies have suggested that dysregulated immune responses, particularly those involving macrophages and neutrophils, contribute to oxidative stress by generating excess reactive oxygen species (ROS) in colon tissues [4, 5]. The subsequent disruption of redox homeostasis by ROS overproduction exacerbates mucosal damage, resulting in epithelial dysfunction and promotes inflammation [6–8]. Therefore, given the critical role of ROS in IBD pathogenesis, ROS-scavenging and anti-inflammatory therapeutic strategies have received increasing attention as potential approaches.

Natural products, such as polyphenols and flavonoids, are increasingly recognised for their strong antioxidant and anti-inflammatory properties and have been proposed as therapeutic agents for ROS-scavenging therapy to modulate the inflammatory response [9, 10]. Quercetin (QCT), a natural product, could potentially treat various inflammatory

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diseases including IBD [11–13]. However, the clinical application remains limited because of poor solubility, limited permeability, and low bioavailability. Tannic acid (TA), which is abundant in various medicinal plants, has extensive physiological effects, including antioxidant, anti-inflammatory, antibacterial, anti-fungal, and anti-tumour actions [14, 15]. In addition, the water-soluble natural polyphenol TA possesses eight gallic acid groups that can interact with various proteins and chelate various metal ions [16–18]. Furthermore, the abundance of hydroxyl groups in TA allows hydrogen bonding with hydrophobic drugs containing carbonyl groups, improving the solubility of poorly soluble drugs [19]. Hence, TA has been used as a pharmaceutical excipient for formulating various drugs [19, 20].

As a chelating agent, QCT has multiple metal-binding sites that can coordinate with various transition metal ions

(e.g. cobalt, zinc, ruthenium, and iron) to form metal complexes [21–23]. Concurrently, TA also possesses excellent chelating ability towards various metal ions (e.g. Fe (II), Ca, and Mn) to facilitate metal–phenolic network formation [18, 24]. In this study, we developed ROS-scavenging, anti-inflammatory TA-Fe-QCT (TFQ) nanocomplexes via a coordination network-based self-assembly process (Fig. 1). The simple reaction between TA, iron chloride (FeCl_2), and QCT produced TFQ nanocomplexes. In this study, we evaluated the in vitro cytotoxicity and the antioxidant and anti-inflammatory effects of TFQ nanocomplexes on inflamed macrophages. We further demonstrated the in vivo therapeutic effects of TFQ nanocomplexes in a mouse model of dextran sulphate sodium (DSS)-induced acute colitis by evaluating the length of the colon tissues, severity of colon damage, and expression of pro-inflammatory cytokines.

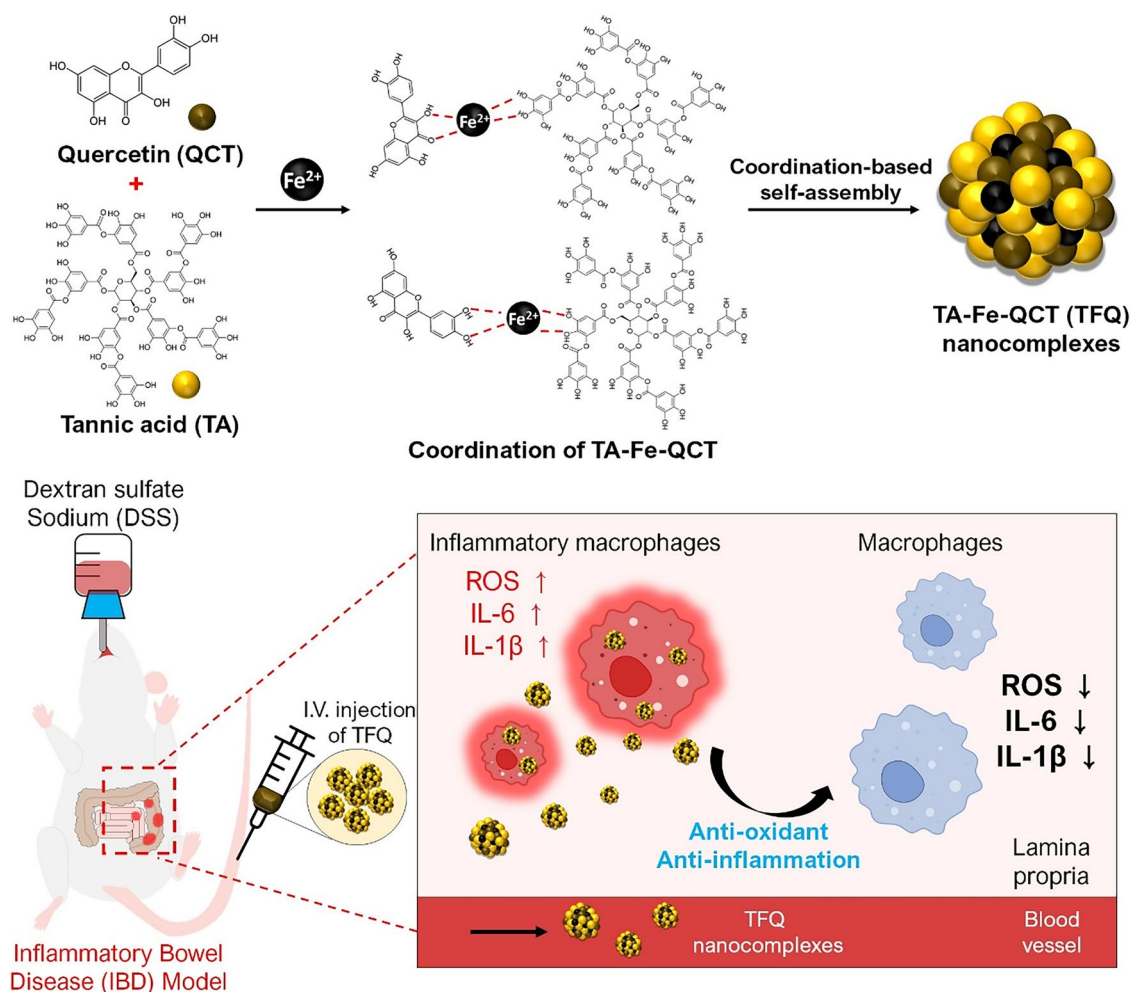


Fig. 1 Schematic illustration of the synthesis process of tannic acid (TA)-iron ion (Fe^{2+})-quercetin (QCT) (TFQ) nanocomplexes via a coordination-based self-assembly process after a simple reaction of TA, Fe, and QCT, and in vivo the therapeutic effects of TFQ nanocomplexes on dextran sulphate sodium (DSS)-induced acute colitis

mouse model. Systemically administered TFQ nanocomplexes possessed antioxidant and anti-inflammatory properties that led to the promising therapeutic responses in the DSS-induced acute colitis mouse model. I.V., Intravenous; ROS, reactive oxygen species; IL, interleukin

2 Materials and methods

2.1 Materials

TA, FeCl_2 , hydrogen peroxide solution (H_2O_2 , 30 wt.% and 34.5 wt.%), potassium bromide (KBr), 2,2-diphenyl-1-picrylhydrazyl (DPPH), potassium persulphate ($\text{K}_2\text{S}_2\text{O}_8$), 2',7'-dichlorofluorescein diacetate (DCFDA), lipopolysaccharide (LPS) from *Salmonella typosa* were purchased from Sigma-Aldrich. QCT, N-acetyl-L-cysteine (NAC), L-ascorbic acid (AA), and 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) diammonium salt (ABTS) were obtained from TCI and Roche Holding AG, respectively. DSS (Mw: 40,000) was purchased from Alfa Aesar. Radioimmunoprecipitation assay (RIPA) buffer and protease inhibitor cocktail were purchased from BIOMAX. Methanol (MeOH), ethanol (EtOH), dimethyl formamide (DMF), and nitric acid (70%) were purchased from SAMCHUN. Dulbecco's modified Eagle medium (DMEM) with or without phenol red, foetal bovine serum (FBS), MEM non-essential amino acid solution (100X), and Dulbecco's phosphate-buffered saline (DPBS) were obtained from Welgene Inc. Dialysis membranes (MWCO: 1 kDa) were purchased from Spectrum Laboratories. Cell counting kit-8 (CCK-8) and EZ-hydrogen peroxide/peroxidase assay kits were procured from Dojindo Molecular Technologies, Inc. and DoGenBio, respectively. Normal saline solution, 0.9% (NS), and 4',6-diamidino-2-phenylindole (DAPI) were obtained from Dai Han Pharm and GBI Labs, respectively.

2.2 Synthesis and characterisations of TFQ nanocomplexes

QCT (35 mg; 118 μmoles) and FeCl_2 (4.3 mg; 34 μmoles) were first dissolved in 10 mL of DMF for 3 h, and then, 10 mL of DMF containing TA (20 mg; 11.8 μmoles) was further added and reacted overnight to prepare TFQ nanocomplexes. The resulting solution was dialysed against deionised water (DW) for 3 days using a cellulose membrane (MWCO: 1 kDa). The prepared TFQ nanocomplexes were sonicated using an ultrasonic processor (KFS-150N; Korea Process Technology Co., Ltd.) and filtered through a cellulose membrane (pore size: 1.2 μm ; Whatman) to remove the large aggregates. Then, the filtered stock solution was stored at 4 °C.

The mean size, Z-average size, and polydispersity index (PDI) were determined under aqueous conditions using a particle size analyser (SZ-100; HORIBA) to confirm the synthesis of TFQ nanocomplexes. The morphology of TFQ nanocomplexes was analysed using field emission

transmission electron microscopy (FE-TEM, JEM-F200; JEOL). Fourier transform infrared (FT-IR) and ultraviolet/visible (UV/Vis) spectroscopies were performed. FT-IR spectra of TA, QCT, and TFQ nanocomplexes were recorded in the range of 4000–400 cm^{-1} using an FT-IR-8400S spectrometer (Shimadzu) and the KBr pellet method. The UV/Vis spectra of TA (0.015625 mg/mL in EtOH), QCT (0.015625 mg/mL in EtOH), and the TFQ nanocomplexes (DW) were obtained using a UV/Vis spectrophotometer (Neo-S450; Neogen). The stock solution of TFQ nanocomplexes (0.125 mL) was diluted in EtOH (0.875 mL), and the absorbance was measured at 278 and 374 nm to determine the loading efficiency of TA and QCT within the TFQ nanocomplexes. The amounts of TA and QCT were calculated using the following equations, which were acquired by the standard curves of TA ($Y = 45.387X + 0.2194$ ($R^2 = 0.99$)) and QCT ($Y = 77.416X + 0.0307$ ($R^2 = 1$)) by measuring the absorbance at 278 or 374 nm with a UV/Vis spectrophotometer (Neo-S450). The Fe content within the TFQ nanocomplexes (1 mL) was determined using an inductively coupled plasma (ICP) spectrometer (Optima 5300 DV; PerkinElmer) after treatment with nitric acid and H_2O_2 .

The storage stability of TFQ nanocomplexes in DW was evaluated. TFQ nanocomplexes dispersed in DW were stored at 20 °C room temperature or 4 °C without any agitation. The mean and Z-average sizes were measured for 1 month using a particle size analyser (SZ-100).

2.3 In vitro antioxidant activity evaluation

The free radical-scavenging capacity of the TFQ nanocomplexes was evaluated using DPPH and ABTS assays according to a previously reported method with minor modifications [25, 26]. First, DPPH radical solution (0.1 mM MeOH, 900 μL) was reacted with various concentrations of TFQ nanocomplexes (50, 100, and 200 $\mu\text{g}/\text{mL}$, 100 μL) under vigorous shaking for 30 min in the dark. As a control, the DPPH radical solution was diluted in MeOH in the same ratio. To compare DPPH radical-scavenging capacity, solutions of TA, NAC, and AA were prepared at 118 μM (corresponding to the estimated TA concentration in 200 $\mu\text{g}/\text{mL}$ of TFQ nanocomplexes), and QCT was prepared at 14 μM (matching the QCT concentration in 200 $\mu\text{g}/\text{mL}$ of TFQ nanocomplexes). Each solution was assessed under identical conditions to ensure a direct comparison of antioxidant activity. The absorbance of each sample was monitored at 517 nm using a UV/Vis spectrophotometer (Neo-S450), and the scavenging activity (%) of the TFQ nanocomplexes was calculated according to Eq. 1:

$$\text{Scavenging capacity (\%)} = \left(1 - \frac{\text{Abs}_{\text{sample}}}{\text{Abs}_{\text{con}}} \right) \times 100. \quad (1)$$

Next, an ABTS radical stock solution was prepared by reacting ABTS (7 mM) with $\text{K}_2\text{S}_2\text{O}_8$ (2.75 mM) (1:1, v/v) overnight. The prepared ABTS radical stock solution was diluted with DW to set the absorbance at 0.7 using a UV/Vis spectrophotometer (Neo-S450). Then, 50 μL of each TFQ nanocomplex (50, 100, and 200 $\mu\text{g}/\text{mL}$) solution was mixed with the prepared ABTS radical solution (3 mL) and incubated under gentle shaking for 10 min in the dark. After the reaction, the absorbance of each solution was measured using a UV/Vis spectrophotometer (Neo-S450). DW (50 μL) without TFQ nanocomplexes was reacted with ABTS radical as the control. The ABTS radical-scavenging capacity was determined using the above equation (Eq. 1).

DW (100 μL) containing TFQ nanocomplexes (0, 50, 100, and 200 $\mu\text{g}/\text{mL}$) was mixed with 100 μL of 100 μM H_2O_2 and incubated for 5 min to assess H_2O_2 scavenging capacity. The amount of H_2O_2 was measured using an EZ-hydrogen peroxide/peroxidase assay kit (DoGenBio Co., Ltd.), and the H_2O_2 scavenging capacity of each group was calculated following the above equation (Eq. 1).

2.4 Cell culture

Macrophages (RAW 264.7) and human intestinal epithelial cells (Caco-2) were purchased from the Korean Cell Line Bank (KCLB). Macrophages were maintained in DMEM (Welgene) supplemented with 10% heat-inactivated FBS and 1% penicillin–streptomycin. Caco-2 were cultured in DMEM containing with 10% FBS, 1% penicillin–streptomycin, and 1% MEM non-essential amino acid solution. All cells were incubated at 37 °C in a humidified 5% CO_2 incubator.

2.5 Cytotoxicity test, in vitro ROS-scavenging activity, and cytoprotective effects of TFQ nanocomplexes on H_2O_2 -induced oxidative stress in macrophages or Caco-2 cells

The in vitro cytotoxicity of TFQ nanocomplexes was evaluated using a CCK-8 assay in three cell models including macrophages, LPS-stimulated macrophages, and Caco-2 intestinal epithelial cells. Macrophages were seeded at 1×10^4 cells/well in 96-well plates and incubated for 24 h. For inflammatory modelling, one group of macrophages was treated with LPS (200 ng/mL) prior to nanocomplex treatment. In parallel, Caco-2 cells were seeded at 2×10^4 cells/well and cultured for 3 days. All cell groups were then treated to TFQ nanocomplexes (0, 10, 20, 50, 100, and 200 $\mu\text{g}/\text{mL}$) for 24 h. After carefully washing the cells with fresh culture medium, CCK-8 reagent solution was added to each well and incubated for an additional 4 h. Absorbance

was measured at 450 nm using a Synergy H1 microplate reader (BioTek). Cell viability was determined as the percentage of viable cells compared with that of the untreated group.

To assess in vitro ROS-scavenging effect of TFQ nanocomplexes on LPS-treated macrophages, macrophages (1×10^4 cells/well) were plated in a 96-well black plate overnight and treated with various concentrations of TFQ nanocomplexes (0, 10, 50, and 100 $\mu\text{g}/\text{mL}$), followed by consecutive addition with LPS (200 ng/mL). After 24 h incubation, cells were treated with DCFDA (50 μM) at 37 °C for 30 min, and the fluorescence intensity of DCFDA (Ex/Em = 485/535 nm) was determined using Synergy H1 microplate reader (BioTek).

Macrophages (1×10^4 cells/well) were seeded in a 96-well plate and incubated overnight for attachment to further verify the cytoprotective effects of TFQ nanocomplexes on H_2O_2 -treated macrophages. Cells were treated with various concentrations of TFQ nanocomplexes (0, 10, 50, and 100 $\mu\text{g}/\text{mL}$, 100 μL) with or without H_2O_2 (500 μM , 100 μL) in DMEM medium for 24 h. After washing the cells with fresh culture medium, the CCK-8 reagent solution was added to each well and further incubated for 4 h. Absorbance was measured at 450 nm using a Synergy H1 microplate reader (BioTek). The protective effect of TFQ nanocomplexes against H_2O_2 -induced oxidative stress in macrophages was expressed as cell viability relative to that of the untreated control group.

2.6 In vitro anti-inflammatory effect of TFQ nanocomplexes on LPS-treated macrophages

Macrophages (1×10^4 cells/well) were incubated in a 96-well plate to assess the in vitro anti-inflammatory effects of TFQ nanocomplexes on LPS-treated macrophages. Then, the cells were activated by treatment with LPS (200 ng/mL) for 30 min, and then TFQ nanocomplexes (0, 10, 50, and 100 $\mu\text{g}/\text{mL}$) were further treated for 24 h. Thereafter, culture supernatants in each group were collected and centrifuged at 1500 rpm for 15 min to remove debris. The concentration of interleukin (IL)-1 β and IL-6 in the culture supernatants was measured using an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's protocols (R&D Systems).

2.7 Animals

All animal experiments and operations conducted in this study were approved by the Institutional Animal Care and Use Committee of Chung-Ang University (202301020090). The in vivo animal experiments were performed in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals. BALB/c mice (6-week-old,

male) were supplied by DooYeol Biotech. The mice were housed in ventilated cages (five mice per cage) and acclimated for 1 week.

2.8 Amelioration of DSS-induced acute colitis in mice by TFQ nanocomplexes

A DSS-induced acute colitis mouse model was established as described previously with a minor modification [27–29]. Briefly, BALB/c mice were fed water containing DSS (4 wt%) daily for 7 days, followed by a change to regular water for an additional day. TFQ nanocomplexes (5 and 20 mg/kg) were administered intravenously to mice once every 2 days (four times in total) for 7 days. The mice were monitored daily during the experimental period according to the criteria for determining the disease activity index (DAI). This reflected the combined scores for body weight loss, rectal bleeding, and stool consistency (Table S1). The mice were killed on day 8, and colon tissues were collected to measure the length of the colon and further assess histology and inflammatory cytokines.

2.9 Histology and inflammatory cytokine assays

The distal sections of collected colons were fixed in 10% buffered formalin, embedded in paraffin, and cross-sectioned into 3 μm slices. Sections were stained with haematoxylin and eosin (H&E) and observed under a light microscope (BX50; Olympus). Images were acquired using an automated slide scanner (TW-SM01; TaeWoong Medical Co. Ltd.).

Frozen distal sections of the colon were mechanically homogenised in cold RIPA buffer containing a protease inhibitor cocktail (Biomax) using a homogeniser (Daihan Science) for the inflammatory cytokine assay. Then, the tissue lysates were centrifuged at 15,000 rpm for 30 min, and the collected supernatant was stored at $-20\text{ }^{\circ}\text{C}$. Total protein in the digestive homogenates was quantified using a BCA assay (Thermo Scientific). The inflammatory cytokine levels of IL-1 β and IL-6 in the supernatant were determined using the ELISA kit (R&D Systems).

2.9.1 Statistical analysis

All data were presented as mean $\pm$ standard deviation (SD). Statistical differences were assessed using a two-tailed Student's *t*-test or one-way ANOVA to compare the means of multiple groups following the Shapiro–Wilk normality test. Statistical analyses were performed using Sigma Plot 15.0 (Systat Software). Statistical significance was set at $p < 0.05$.

3 Results and discussion

3.1 Synthesis and characterisations of TFQ nanocomplexes

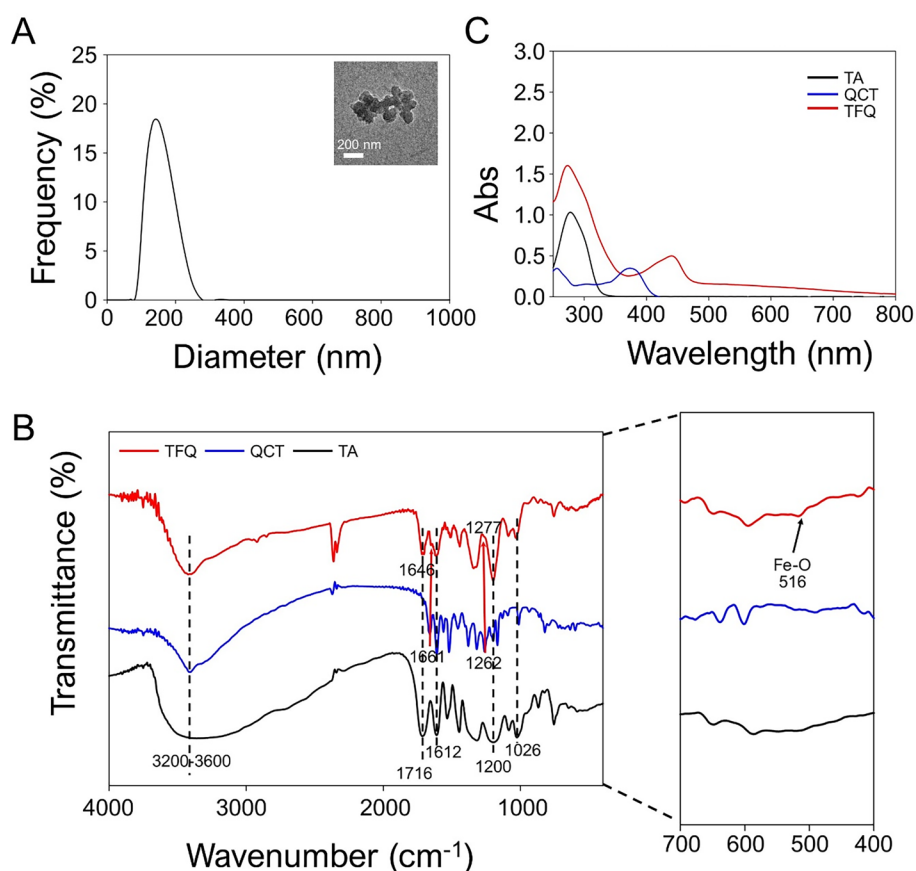
TA, a naturally derived polyphenol, facilitates the fabrication of a coordination network-based self-assembly of TA and metal ions because of its ability to chelate various metal ions, known as metal–phenolic networks [18, 24]. As a chelating agent, QCT can form complexes with transition metal ions [21–23]. Based on reports that TA and QCT can coordinate with metal ions, we synthesised TFQ nanocomplexes via a coordination-based self-assembly process after a simple reaction of TA, QCT, and Fe (Fig. 1).

We analysed the size distributions and morphology of TFQ nanocomplexes using dynamic light scattering (DLS) and TEM to verify their synthesis. The measured hydrodynamic mean and Z-average sizes of the TFQ nanocomplexes were $141.7 \pm 33.5\text{ nm}$ and 150.2 nm , respectively, with a mid-range of PDI value of 0.301 (Fig. 2A). The TEM images revealed that the obtained TFQ nanocomplexes exhibited near-spherical shapes with sizes ranging from 150 to 200 nm, which was consistent with the DLS measurements. In addition, the TFQ nanocomplexes showed a stable size distribution in DW without significant changes in the Z-average size, and their hydrodynamic mean sizes were consistently maintained during storage for over 30 d (Fig. S1). This indicated excellent water dispersity and colloidal stability.

FT-IR data revealed that all the TA, QCT, and TFQ nanocomplexes exhibited broad bands for the O–H stretching vibration ($3200\text{--}3600\text{ cm}^{-1}$) (Fig. 2B, Table S2). QCT showed characteristic peaks at 1661 cm^{-1} (C=O stretching) and 1262 cm^{-1} (C–O–C stretching). However, these two peaks in QCT shifted slightly to 1646 cm^{-1} and 1277 cm^{-1} in the TFQ nanocomplexes, indicating the formation of coordination between QCT and metal ions [25, 30, 31]. Most of the characteristic vibration peaks of TA and TFQ nanocomplexes were similar. Notably, a new characteristic Fe–O stretching vibration peak at 516 cm^{-1} was detected in the TFQ nanocomplexes. In contrast, QCT and TA showed no such bands, suggesting the formation of a metal coordination-based TFQ self-assembly.

The formation of TFQ nanocomplexes was further confirmed using UV/Vis spectroscopy. As shown in the UV/Vis spectra (Fig. 2C), TA and QCT showed main characteristic peaks at 278 nm (for TA) and 372 nm (for QCT), respectively, in accordance with the previous literature [32, 33]. In addition, a characteristic peak at 278 nm in TA was observed in the UV/Vis spectrum of the TFQ nanocomplexes. The formation of TFQ nanocomplexes

Fig. 2 Characterisations of TFQ nanocomplexes. **A** Size distribution and transmission electron microscopy image (inset) of TFQ nanocomplexes. Scale bar = 200 nm. **B** Fourier transform infrared and **C** ultraviolet/visible spectra of TA, QCT, and TFQ nanocomplexes. TFQ, Tannic acid (TA)-iron ion (Fe^{2+})-quercetin (QCT)



was confirmed by the shift of the absorption peak in QCT from 372 to 440 nm due to the complexation of Fe^{2+} ions with both OH at the C3 and C=O at the C4 position [25] as well as by the appearance of a broad charge transfer band at over 400 nm due to the coordination complex between TA and Fe^{2+} [26]. These results suggested that the TFQ nanocomplexes were formed through the coordination networks of Fe^{2+} with both TA and QCT.

The amounts of TA, QCT, and Fe^{2+} within the TFQ nanocomplexes were determined using UV/Vis and ICP analyses. Based on the standard curves for TA and QCT, 1 mL of TFQ nanocomplex solution contained $127.8 \pm 27.3 \mu\text{g}$ ($75.1 \mu\text{mol}$, 1701 g/mol) of TA and $26.7 \pm 7.3 \mu\text{g}$ ($88.3 \mu\text{mol}$, 302.2 g/mol) of QCT, respectively. Furthermore, ICP analysis confirmed that 1 mL of TFQ nanocomplex solution contained $5.9 \pm 1.6 \mu\text{g}$ ($105.7 \mu\text{mol}$, 55.8 g/mol) of Fe^{2+} . Based on these results, the stoichiometry of TA: Fe^{2+} :QCT in the nanocomplexes was determined to be approximately 1:1.4:1.2.

3.2 In vitro antioxidant activity of TFQ nanocomplexes

Oxidative stress, mediated by excessive production of free radicals and ROS, is one of the main pathological processes involved in the progression of IBD [4, 5, 34]. Previous

studies have reported that polyphenol-based antioxidant nanomedicines could inhibit inflammation through free radicals and ROS scavenging, ultimately enhancing IBD therapeutic outcomes [35]. Hence, we first investigated the in vitro radical-scavenging activity of TFQ nanocomplexes using DPPH and ABTS radicals [36–38]. TFQ nanocomplexes dose-dependently inhibited $28.5 \pm 0.6\%$, $49.9 \pm 2.0\%$, and $81.3 \pm 0.4\%$ of DPPH radicals at 50, 100, and 200 $\mu\text{g/mL}$ of TFQ nanocomplexes, respectively (Fig. 3A). Consistent with DPPH assay, TFQ nanocomplexes at 50, 100, and 200 $\mu\text{g/mL}$ concentrations significantly reduced $25.9 \pm 0.6\%$, $47.8 \pm 0.3\%$, and $83.2 \pm 0.4\%$ of ABTS radicals, respectively (Fig. 3B). The in vitro ROS-scavenging activity of TFQ nanocomplexes was further investigated by measuring H_2O_2 levels after the reaction of TFQ nanocomplexes with 100 μM H_2O_2 . As shown in Fig. 3C, TFQ nanocomplexes effectively reduced H_2O_2 levels dose-dependently. The H_2O_2 scavenging capacities of TFQ nanocomplexes were measured at concentrations of 50, 100, and 200 $\mu\text{g/mL}$, yielding values of $37.0 \pm 9.2\%$, $63.4 \pm 0.0\%$, and $70.5 \pm 3.1\%$, respectively. The antioxidant activity of TFQ nanocomplexes was further compared with that of TA, QCT, NAC, and AA, representative ROS scavengers [26]. NAC and AA exhibited DPPH scavenging capacities of $11.0 \pm 0.4\%$ and $40.7 \pm 0.5\%$, respectively, which are weak or comparable to the activity

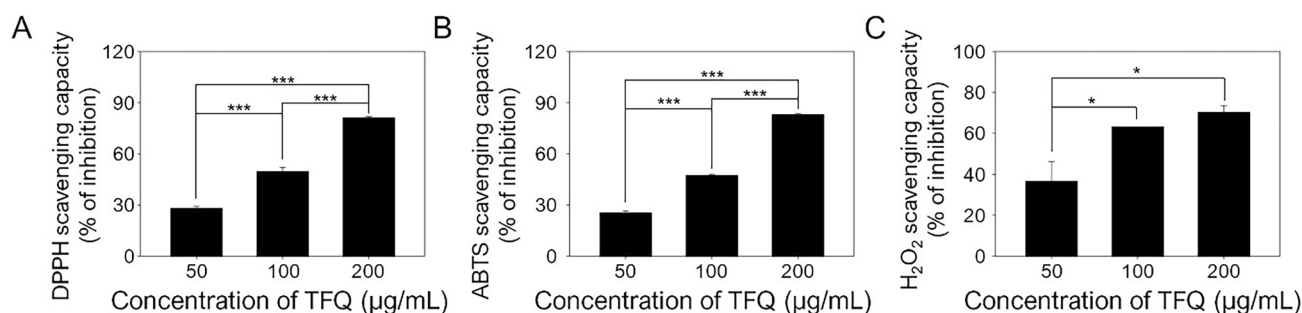


Fig. 3 In vitro reactive oxygen species-scavenging capacity of TFQ nanocomplexes. **A** 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and **B** 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) diammonium

salt (ABTS) assays and **C** H₂O₂ scavenging ability of TFQ nanocomplexes at various concentrations. ($n=3/\text{group}$). * $p<0.05$; and *** $p<0.001$. TFQ, Tannic acid-Fe²⁺-quercetin

observed for 50 µg/mL TFQ nanocomplexes (Figs. 3A, S2). QCT inhibited $35.9 \pm 1.9\%$ of DPPH radicals, while TA reduced $74.4 \pm 1.0\%$, similar to the scavenging capacity of 200 µg/mL TFQ nanocomplexes. Notably, although TA and QCT are coordinated with Fe²⁺ in the TFQ nanocomplexes, their antioxidant activities are largely preserved or even enhanced, resulting in more effective ROS scavenging than other tested antioxidants. This demonstrated that TFQ nanocomplexes can effectively scavenge free radicals and H₂O₂, indicating their excellent antioxidant effects against free radicals and ROS.

3.3 Cytotoxicity, in vitro ROS-scavenging activity, and cytoprotective effects of TFQ nanocomplexes on H₂O₂-induced oxidative stress in macrophages or Caco-2 cells

The in vitro cytotoxicity of TFQ nanocomplexes was examined in macrophages, LPS-stimulated macrophages, and Caco-2 cells. Figure 4A shows that macrophages,

LPS-stimulated macrophages, and Caco-2 cells maintained above 90% cell viability at all tested concentrations of the nanocomplexes, indicating that the TFQ nanocomplexes were biocompatible and had no cytotoxic effects on the tested macrophages and Caco-2 cells.

Macrophages treated with various concentrations of TFQ nanocomplexes were treated with LPS, which overproduces ROS in macrophages [39, 40], to verify in vitro ROS-scavenging activity. The in vitro ROS-scavenging effect of TFQ nanocomplexes on LPS-stimulated macrophages was demonstrated by detecting intracellular ROS levels using a well-established indicator DCFDA dye, which is turned into a relatively weak fluorescent 2',7'-dichlorodihydrofluorescein (DCFH) into the cells, whereas DCFH is transformed into the strongly fluorescent 2',7'-dichlorofluorescein (DCF) by overproduced ROS in LPS-stimulated macrophages [41–43]. Compared with the weak fluorescence signal in untreated macrophages, LPS-stimulated macrophages showed significantly increased fluorescence intensity (Fig. 4B). The strong fluorescence

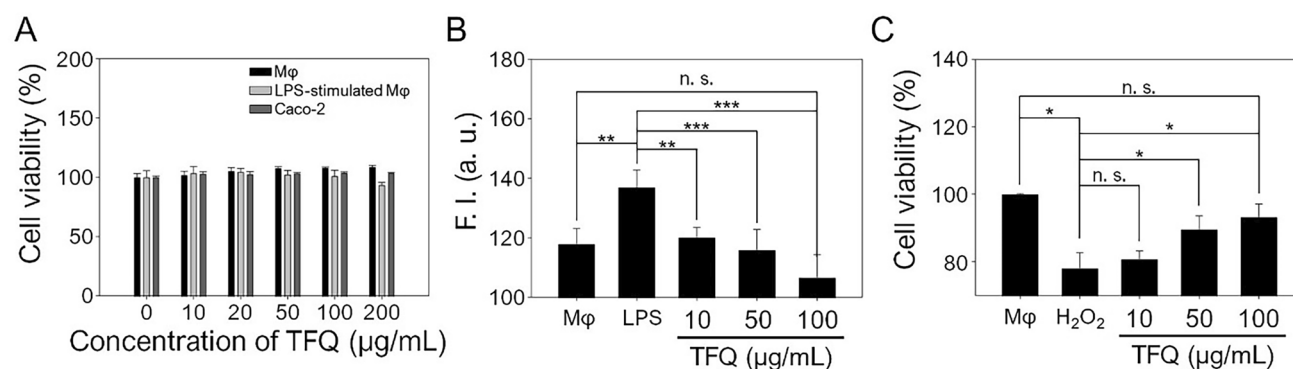


Fig. 4 **A** In vitro cytotoxicity of TFQ nanocomplexes towards macrophages, lipopolysaccharide (LPS)-stimulated macrophages, and Caco-2 cells ($n=5/\text{group}$). **B** In vitro reactive oxygen species-scavenging effect of TFQ nanocomplexes against LPS-stimulated macrophages using DCFDA dye ($n=4/\text{group}$). ** $p<0.01$; *** $p<0.005$.

C In vitro cytoprotective effects of TFQ nanocomplexes against H₂O₂-induced oxidative stress in macrophages ($n=3/\text{group}$). * $p<0.05$. TFQ, Tannic acid-Fe²⁺-quercetin; DCFDA, 2',7'-dichlorofluorescein diacetate; n.s., not significant

intensity in LPS-stimulated macrophages decreased remarkably with increasing concentrations of TFQ nanocomplexes, indicating their potent ROS-scavenging effects against ROS-overexpressing macrophages.

As a powerful oxidising agent, exogenous H_2O_2 -induced oxidative stress at the cellular level, ultimately causing cytotoxicity against the cells [44, 45]. As shown in Fig. 4C, compared to the viability of non-treated macrophages, exogenous treatment of 500 μM H_2O_2 significantly reduced cell viability because excess amount of H_2O_2 caused oxidative impairment to cellular parts, leading to cell apoptosis [46, 47]. However, TFQ nanocomplexes remarkably protected the viability of H_2O_2 -treated macrophages in a dose-dependent manner. This implied that TFQ nanocomplexes effectively reduced H_2O_2 -induced oxidative stress in macrophages owing to their excellent antioxidant effects, leading to cytoprotective effects against H_2O_2 -induced oxidative stress.

3.4 In vitro anti-inflammatory effect of TFQ nanocomplexes on LPS-treated macrophages

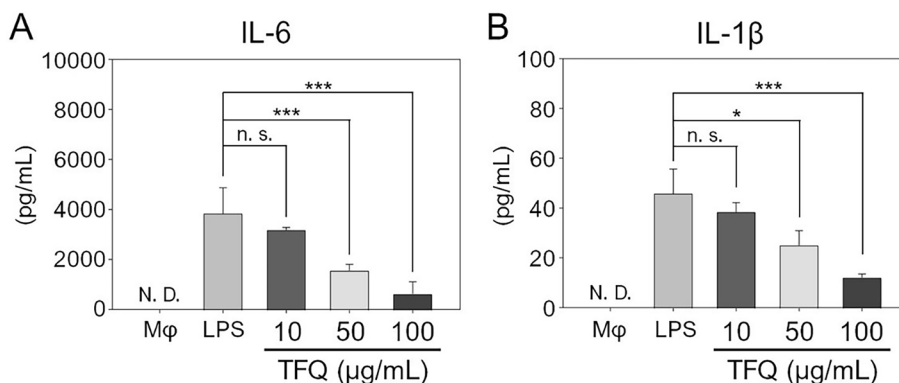
Because the overexpression of ROS in LPS-stimulated cells upregulated pro-inflammatory cytokines (e.g. IL-6 and IL-1 β), ultimately exacerbating inflammatory responses [48, 49], macrophages were treated with LPS to induce inflammatory environments. Hence, the in vitro anti-inflammatory effects of TFQ nanocomplexes on LPS-stimulated cells were assessed by measuring IL-6 and IL-1 β levels. Compared with normal macrophages without expressing IL-6 and IL-1 β , LPS-stimulated macrophages showed remarkably upregulated IL-6 and IL-1 β levels (Fig. 5). However, TFQ nanocomplexes at 50 $\mu g/mL$ and 100 $\mu g/mL$ concentrations significantly inhibited such pro-inflammatory cytokines in LPS-stimulated macrophages ($*p < 0.05$ and $***p < 0.005$ versus LPS-treated macrophages), implying that TFQ nanocomplexes had effective anti-inflammatory effects against LPS-stimulated

macrophages, which is associated with their ROS-scavenging activity (Fig. 4).

3.5 In vivo therapeutic effects of TFQ nanocomplexes on DSS-induced acute colitis mouse model

Considering the antioxidant and anti-inflammatory effects of the TFQ nanocomplexes, we examined the in vivo therapeutic effects of the TFQ nanocomplexes in a mouse model of DSS-induced acute colitis. To assess the in vivo therapeutic effects, the mice received TFQ nanocomplexes intravenously at 5 and 20 mg/kg once every 2 days during treatment with water containing 4% DSS for 7 days, whereas the control and DSS groups did not receive any nanocomplexes (Fig. 6A). Figure 6B shows that the DAI score of the DSS group steadily increased, unlike that of the control group. In contrast, mice administered TFQ nanocomplexes at 20 mg/kg showed a noticeable decrease in DAI score and amelioration of IBD symptoms compared to those administered DSS alone. Compared to the control group (9.7 ± 0.3 cm), the colon length of the DSS group was remarkably reduced (6.96 ± 0.7 cm) (Fig. 6C). However, the colon length increased to 8.4 ± 0.3 cm after treatment with 20 mg/kg of TFQ nanocomplexes compared to that in the DSS group. These results indicated that treatment with 20 mg/kg TFQ nanocomplexes effectively prevented colon shortening in an acute colitis mouse model. Moreover, histological analysis revealed that the control group had a healthy colonic mucosal structure without any signs of mucosal damage, whereas the DSS group exhibited severe destruction of mucous membranes, depletion of epithelial cells, and infiltration of immune cells, which are representative symptoms of DSS in mice [50–52] (Fig. 6D). In contrast, treating TFQ nanocomplexes attenuated the DSS-induced inflammatory changes greatly and the severity of the colon damage compared with the DSS group. The pro-inflammatory cytokines, including IL-6 and IL-1 β , in the colon tissues of mice were measured using ELISA to further demonstrate the therapeutic effects

Fig. 5 In vitro anti-inflammatory effects of TFQ nanocomplexes against lipopolysaccharide (LPS)-stimulated macrophages. Levels of pro-inflammatory cytokines, including **A** IL-6 and **B** IL-1 β , secreted by LPS-stimulated macrophages determined using an ELISA kit. ($n = 3/\text{group}$). $*p < 0.05$ and $***p < 0.005$. TFQ, Tannic acid- Fe^{2+} -quercetin; IL, Interleukin; N.D., No detection; n.s., Not significant



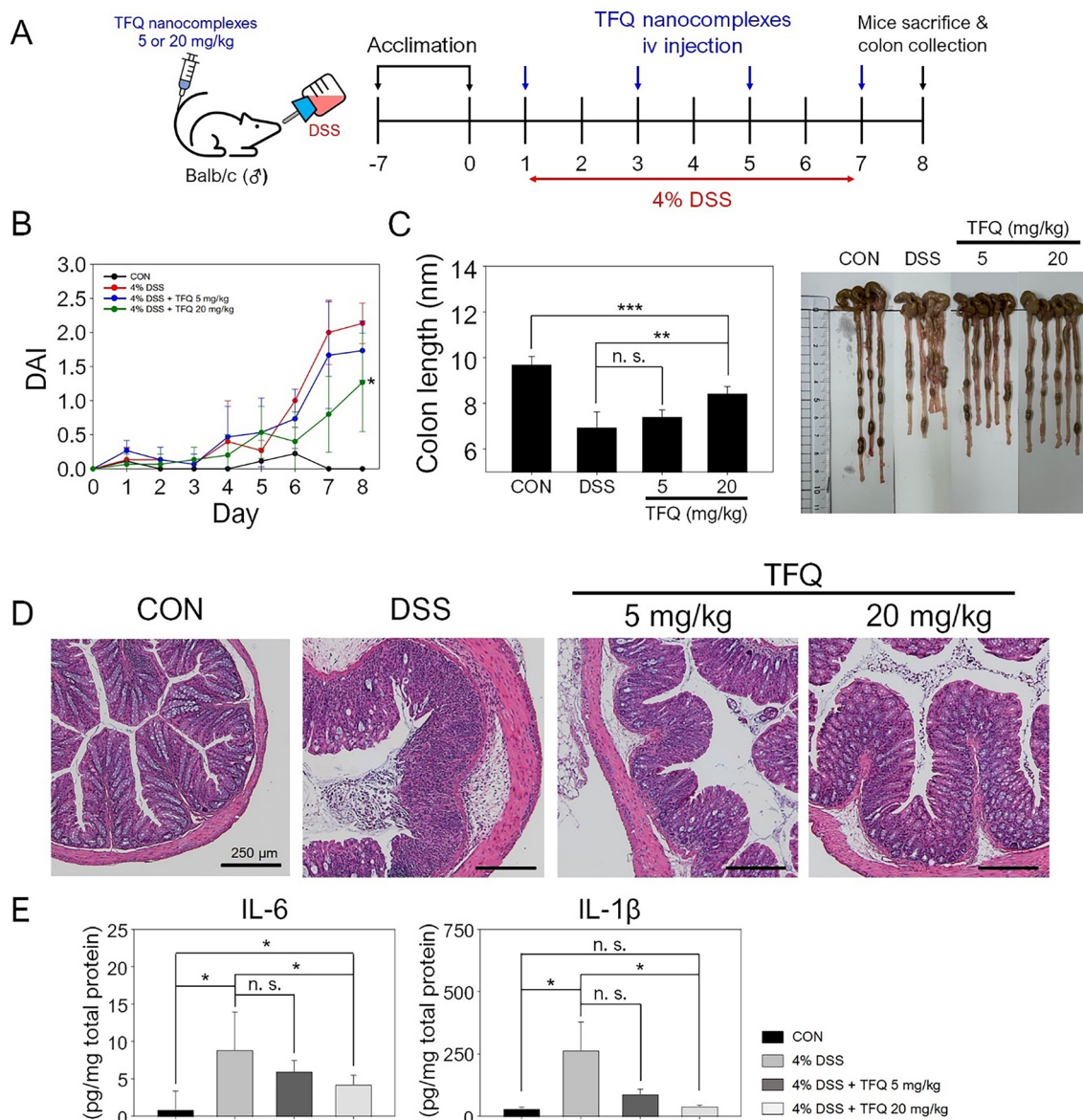


Fig. 6 In vivo therapeutic effects of TFQ nanocomplexes on DSS-induced acute colitis mouse model. **A** Overall experimental scheme for the treatment with TFQ nanocomplexes during the preparation period of DSS-induced acute colitis mouse model. **B** Disease activity indexes (DAI) throughout the entire experimental period. $*p < 0.05$. **C** Colon lengths and images on day 8. $**p < 0.01$; $***p < 0.005$. **D**

H&E staining of colon sections from each group. Scale bar = 250 μ m. **E** Levels of pro-inflammatory cytokines representative to IL-6 and IL-1 β in the colon tissue of each experimental group. (CON, $n = 3$; DSS, TFQ 5 mg/kg or 20 mg/kg, $n = 5$ /group). $*p < 0.05$. TFQ, Tanic acid-Fe²⁺-quercetin; DSS, dextran sulphate sodium; IL, interleukin, I.V., intravenous; n.s., not significant

of TFQ nanocomplexes because the abnormal secretion of such cytokines is associated with IBD progression [48, 53]. Compared with the control group, the DSS group significantly induced inflammation and increased the expression of IL-6 and IL-1 β (Fig. 6E). Notably, treatment with 20 mg/kg TFQ nanocomplexes effectively inhibited the secretion of such pro-inflammatory cytokines, which were nearly restored to normal levels. Overall, these results suggested that the ROS-scavenging anti-inflammatory TFQ nanocomplexes have promising therapeutic responses in

IBD due to their excellent antioxidant and anti-inflammatory effects.

4 Conclusion

In this study, we developed ROS-scavenging, anti-inflammatory TFQ nanocomplexes for treating IBD via a coordination-based self-assembly process after a simple reaction between TA, QCT, and Fe. The prepared TFQ

nanocomplexes possessed remarkable antioxidant activity towards free radicals and ROS such as H₂O₂. Furthermore, biocompatible TFQ nanocomplexes showed the in vitro potent ROS-scavenging effects against ROS-over-expressing macrophages and cytoprotective effects against H₂O₂-induced oxidative stress in macrophages. Moreover, our findings revealed that TFQ nanocomplexes could alleviate disease symptoms such as colon shortening and inflammation, leading to promising therapeutic responses in a DSS-induced acute colitis mouse model.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All animal experiments and operations conducted in this study were approved by the Institutional Animal Care and Use Committee of Chung-Ang University (202301020090).

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