

Bio-inspired helical microcarriers anchoring quercetin nanoparticles enable prolonged and self-trackable colonic delivery in colitis

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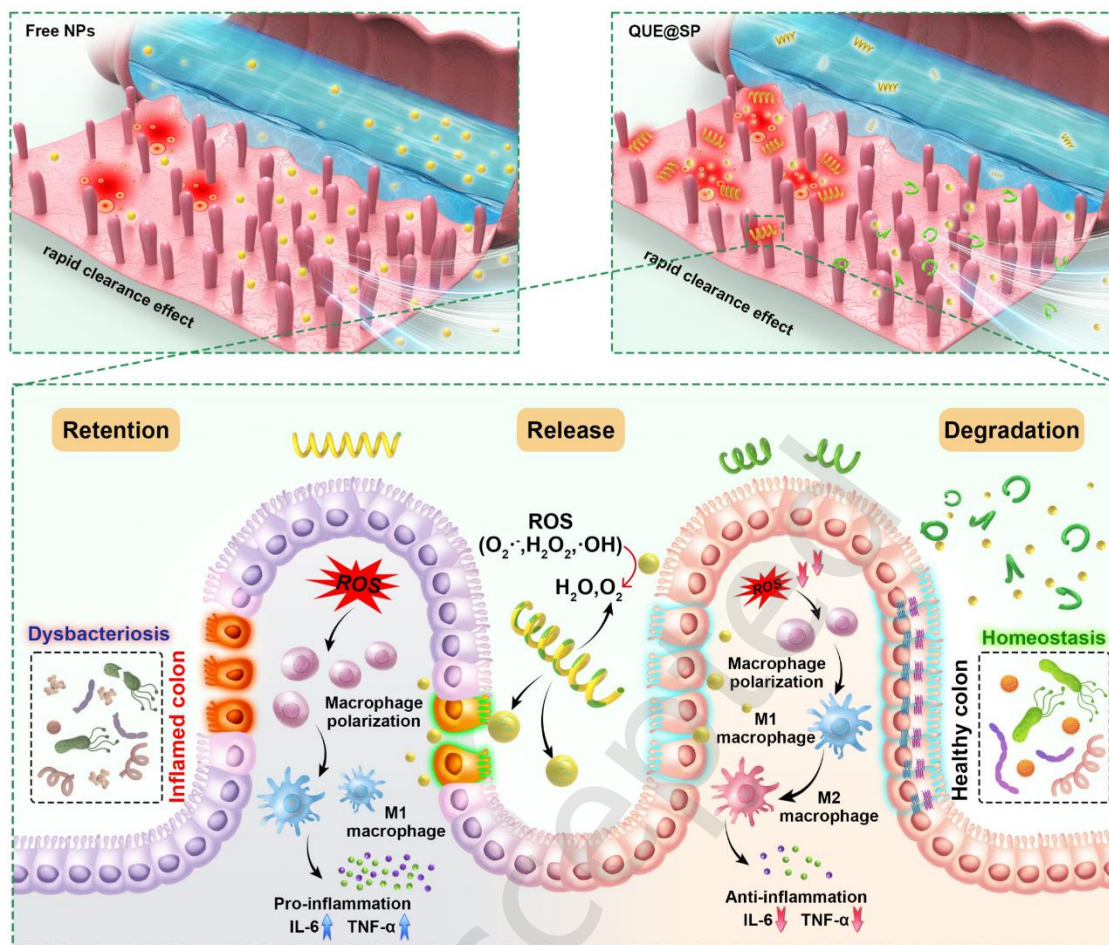
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Bio-inspired quercetin nanoparticle-anchored helical microcarriers were developed for self-trackable and targeted colitis therapy by inducing shape-driven mucosal retention, scavenging reactive oxygen species, remodeling macrophage polarization, and restoring the intestinal barrier.

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ABSTRACT: Oral antioxidant therapy for Inflammatory Bowel Disease (IBD) is currently hampered by the “oral delivery paradox”, wherein the therapeutic potential of bioactive agents is compromised by poor aqueous solubility and rapid gastrointestinal washout. To overcome these biopharmaceutical barriers, we engineered a bio-inspired theranostic platform (QUE@SP) via the electrostatic anchoring of cationic, quercetin-loaded zein/chitosan nanoparticles onto the surface of the natural helical microcarrier, *Spirulina platensis* (SP). Mechanistically, the biomimetic helical morphology of SP induces a hydrodynamic locking effect within the intestinal villi, transforming the transient transit of nanoparticles into a sustained mucosal depot. Following mucosal attachment, the controlled release of quercetin is driven by microbiota-triggered enzymatic degradation of the chitosan-zein matrix, ensuring site-specific drug discharge. *In vivo* evaluations demonstrated a prolonged colonic retention of up to 48 hours, which maximized localized drug exposure. This translated into potent reactive oxygen species (ROS) scavenging, macrophage polarization, and the restoration of intestinal barrier integrity in colitis murine models. Furthermore, as an inherently biocompatible carrier, SP facilitated self-trackable monitoring of mucosal distribution via its intrinsic fluorescence, followed by complete biodegradation and nutritional absorption. Ultimately, this work introduces a shape-driven paradigm that repurposes natural microalgae into a precision oral vehicle, providing a biologically integrated strategy for targeted colitis therapy.

KEYWORDS: inflammatory bowel disease, helical microcarrier, shape-dependent retention, ROS scavenging, quercetin

1 Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, represents a formidable global health challenge characterized by relentless, relapsing inflammation of the gastrointestinal tract (GIT) [1, 2]. While the etiology involves a complex interplay of immunity and microbiota, the uncontrolled surge of reactive oxygen species (ROS) is increasingly recognized as a pivotal instigator of mucosal destruction [3-5]. This ROS storm perpetuates oxidative stress, amplifies inflammatory cascades, and hinders mucosal healing [6]. Consequently, scavenging excessive ROS is a promising strategy to break this vicious cycle [7]. However, current clinical pharmacotherapies (e.g., corticosteroids and immunosuppressants) face a severe therapeutic dilemma [8]. Due to IBD-associated diarrhea and rapid colonic transit, orally administered drugs suffer from accelerated elimination and insufficient retention at the inflamed sites. To compensate for this “washout effect”, high doses are often required, inevitably leading to debilitating systemic toxicity and non-specific distribution [9-11]. Moreover, traditional treatments lack the capability for real-time, non-invasive monitoring of drug accumulation in the deep gut [12, 13]. Therefore, there is an urgent unmet need to develop

precision oral platforms that simultaneously achieve prolonged colonic retention, targeted ROS scavenging, and visualized tracking of therapeutic distribution to effectively manage colitis [14].

To construct such an advanced therapeutic platform, selecting an appropriate antioxidative payload is the primary prerequisite. Natural flavonoid compounds, such as baicalin, puerarin, and epigallocatechin gallate, have emerged as potent candidates for IBD management [15-17]. Among this class, Quercetin (QUE) stands out as a preeminent therapeutic agent [18]. Beyond simple scavenging, QUE exhibits a broad therapeutic spectrum, effectively modulating immune responses and promoting mucosal healing, making it an ideal agent for mitigating the pathological oxidative microenvironment in the gut [19, 20]. However, the clinical translation of this pleiotropic therapeutic agent faces a formidable biopharmaceutical barrier. QUE is notoriously plagued by an oral delivery paradox: its immense biological potential is nullified by its extremely poor water solubility (< 0.01 mg/mL) and rapid metabolism in the gastrointestinal environment [21-23]. Upon oral administration, naked quercetin is extensively subjected to presystemic clearance and auto-oxidation before it can reach the inflamed colon in effective concentrations. Consequently, the bioavailability at the target site is negligible. To rescue this potent agent from

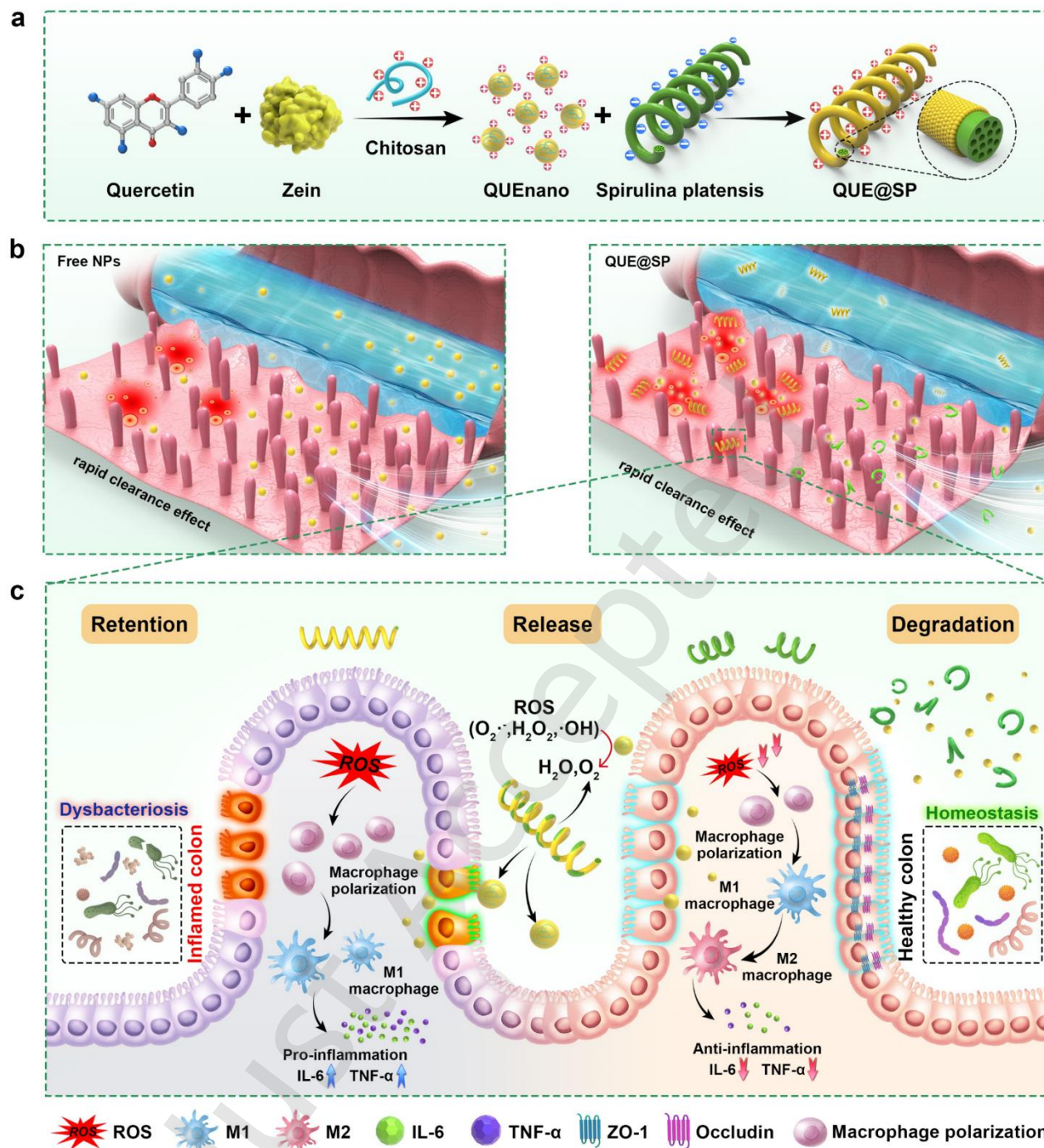


Figure 1 Schematic illustration of the QUE@SP microalgae-based drug carrier and the *in vivo* therapeutic mechanism. (a) Preparation process of quercetin nanoparticles and their subsequent loading onto *Spirulina platensis*. (b) Schematic comparison of the rapid gastrointestinal washout of free nanoparticles and the prolonged villous retention of QUE@SP via hydrodynamic locking. (c) Mechanism of ROS scavenging and colitis treatment mediated by the QUE@SP microalgae drug carrier.

physiological elimination and unlock its full utility, there is a critical need for an advanced delivery vehicle, one that not only enhances its aqueous dispersibility but also shields it through the harsh GIT environment to ensure precise accumulation at the target site, thereby bridging the gap between its potent bioactivity and poor biopharmaceutical performance [24, 25]. Recently, surface-engineering strategies have demonstrated tremendous success in protecting living biological carriers against harsh gastrointestinal fluids, significantly enhancing their oral delivery efficiency and therapeutic outcomes in colitis [26–28]. These bacteria/nanomaterial hybrid systems have emerged as a powerful paradigm in precision medicine, demonstrating exceptional capabilities in navigating

complex pathological environments, continuously scavenging oxidative stress, and orchestrating the restoration of gut microbiota [29, 30]. Inspired by these biointerfacial successes, we sought to combine advanced surface engineering with uniquely structured natural bio-carriers.

While synthetic vectors (e.g., polymers and liposomes) have been extensively utilized, most of these conventional vehicles feature a spherical morphology, making them highly susceptible to rapid gastrointestinal washout—a biopharmaceutical barrier drastically exacerbated by IBD-associated diarrhea. Consequently, natural microalgae have recently garnered significant attention as promising functional biomaterials for tissue repair and bio-carriers,

distinguishing themselves through their renewable nature, inherent antioxidant properties, abundant surface functional groups, and versatile bio-architectures [13, 31-33]. While various algal species such as *Chlamydomonas reinhardtii* and diatoms have been explored, *Spirulina platensis* (SP) stands out as a superior candidate specifically for colitis therapy. Distinguished from synthetic materials that often raise biocompatibility concerns, SP offers a natural, evolutionarily optimized framework. Drawing inspiration from the colonization strategy of helical enteric pathogens (e.g., *Helicobacter pylori*), SP possesses a distinctive spiral architecture (100–200 μm) [34, 35]. Unlike common spherical microalgae or nanoparticles that easily slide over the mucosa, this biomimetic morphology offers a distinct hydrodynamic advantage. Studies suggest that such anisotropic shapes enhance mucoadhesion and resist fluid shear stress more effectively than spheres through geometric entrapment within the intestinal villi [36, 37]. This shape-dependent retention mechanism significantly prolongs the colonic residence time. Furthermore, SP exhibits intrinsic red fluorescence derived from its structural chlorophyll, conferring a robust self-tracking capability. By eliminating the need for additional chemical labeling, this natural autofluorescence elegantly bypasses the inherent drawbacks of traditional synthetic dyes—such as premature leakage, false-positive imaging artifacts, and potential cytotoxicity [38-40]. Thus, SP serves as a versatile natural microcarrier that seamlessly integrates improved bioavailability with highly reliable diagnostic potential.

In this study, we engineered a bio-inspired oral delivery system, QUE@SP, via a facile electrostatic self-assembly strategy, wherein hydrophobic quercetin was encapsulated into cationic chitosan-coated zein nanoparticles to achieve robust adsorption onto the natural helical microcarrier [41]. This design integrates structural anchoring with molecular therapeutics. Specifically, zein provides a hydrophobic core to encapsulate poorly soluble QUE, while the chitosan shell facilitates electrostatic anchoring onto SP and enhances mucin adhesion. Mechanistically, the evolved helical architecture confers a hydrodynamic locking effect within the inter-villus niches, transforming the typically transient transit of nanoparticles into a sustained mucosal depot. This spatial anchoring maximizes the interaction interface between the therapeutic cargo and the inflamed epithelium. Following mucosal attachment, the system is specifically designed to harness the well-documented microbiota-triggered enzymatic degradation of the chitosan-zein matrix, thereby facilitating site-specific drug discharge within the inflamed microenvironment [42-45].

By exploiting this bio-inspired hydrodynamic locking, we hypothesized that the QUE@SP system would effectively overcome the gastrointestinal washout effect to maximize localized drug exposure. *In vivo* evaluations validated this rationale, demonstrating a prolonged colonic retention of up to 48 hours and exhibiting a fluorescence intensity approximately 4.6 times that of carrier-free nanoparticles. Importantly, from a clinical perspective, this prolonged colonic residence is envisioned to break the current therapeutic dilemma of frequent daily dosing, offering a highly patient-compliant strategy for chronic colitis management. Concurrently, at the pathological level, this extended residence translated into effective ROS scavenging, restored intestinal barrier integrity, and re-established microenvironmental homeostasis. Unlike synthetic vectors that may impose metabolic burdens, SP functions as an inherently biocompatible carrier, offering non-invasive self-tracking via intrinsic fluorescence followed by complete nutritional absorption [46, 47]. Ultimately, this work introduces an edible theranostic paradigm that repurposes natural microalgae into a precision oral vehicle, providing a visualized, clinically translatable, biologically integrated strategy for colitis therapy.

2 Experimental sections

2.1 Materials

Spirulina platensis (SP) was obtained from Shanghai Guangyu Biological Technology Co., Ltd. (Shanghai, China) and cultured in Zarrouk's medium. Quercetin (purity $\geq 97\%$) and dextran sulfate sodium (DSS, MW: 40,000 Da) were purchased from Macklin Biochemical Co., Ltd. (Shanghai, China). Chitosan hydrochloride (degree of deacetylation: 80.0–90.0%) was acquired from Rhawn (Shanghai, China). Zein was purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). Enzyme-linked immunosorbent assay (ELISA) kits for mouse Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF- α) were obtained from Beijing Biotopped Technology Co., Ltd. (Beijing, China). IEC-6 cells (Cat. No. SC0621) were obtained from Yuchi Biotechnology Co., Ltd. (Shanghai, China), and RAW 264.7 cells (Cat. No. FH0328) were purchased from Shanghai Fuheng Biotechnology Co., Ltd. (Shanghai, China). Primary antibodies against MPO (Cat. No. GB11224), ZO-1 (Cat. No. GB111402), and Occludin (Cat. No. GB111401) were purchased from Servicebio (Wuhan, China), while anti-CD86 (Cat. No. 30691-1-AP) and anti-CD163 (Cat. No. 31024-1-AP) antibodies were obtained from Proteintech Group (Wuhan, China). For immunofluorescence detection, FITC-conjugated goat anti-rabbit IgG and Cy3-conjugated goat anti-rabbit IgG (Servicebio, Wuhan, China) were used as secondary antibodies. All other reagents were obtained from commercial suppliers and used as received.

2.2. Cultivation of *Spirulina platensis*

Spirulina platensis (SP) was incubated in Zarrouk's liquid medium at 30 °C with constant agitation on a rotary shaker (120 rpm). A 12-h/12-h alternating light-dark photoperiod with an illumination intensity of 4000 lux was applied during the growth phase. Upon completion of cultivation, the microalgal biomass was harvested via centrifugation (3000 rpm, 10 min). The collected cellular pellet was thoroughly rinsed with ultrapure water to remove residual medium and subsequently lyophilized for future use.

2.3. Preparation of quercetin nanoparticles

Quercetin-loaded nanoparticles were fabricated using a modified antisolvent precipitation method based on a previously reported protocol. Briefly, quercetin (20 mg) and zein (400 mg) were dissolved in 20 mL of 80% (v/v) ethanol to form the organic phase (mass ratio of QUE: zein = 1:20). This solution was then injected dropwise (within 1 min) into an aqueous solution of chitosan hydrochloride (5 mg/mL) under magnetic stirring at 1000 rpm. The mixture was stirred for an additional 30 min to ensure thorough self-assembly. Subsequently, the suspension was centrifuged (2000rpm, 10min) to remove large aggregates, and the supernatant was collected. Ethanol was removed from the supernatant using a rotary evaporator under reduced pressure at 50 °C, followed by volume replacement with an equal amount of ultrapure water. Finally, the aqueous suspension was lyophilized to obtain the QUE@nano powder. For the preparation of fluorescently labeled nanoparticles, FITC dissolved in dimethyl sulfoxide (DMSO) was added to the initial 80% ethanol solution containing quercetin and zein. All other procedures remained identical to those described above.

2.4. Preparation of microalgae-based drug carrier (QUE@SP)

The lyophilized QUE nanoparticles were re-suspended in 20 mL of ultrapure water. Subsequently, lyophilized SP powder was added to the suspension at a mass ratio of 2:1 (SP to QUE@nano). The mixture was stirred at room temperature for 6 min to facilitate adsorption. Afterward, the suspension was centrifuged at 1000 rpm (5 min) to remove the supernatant containing unbound QUE@nano. The resulting pellet was collected and lyophilized to yield the final microalgae-based drug carrier, designated as QUE@SP.

2.5. Morphological evolution of QUE@SP in simulated gastrointestinal fluids

To simulate the behavior of the drug carriers in the

gastrointestinal tract, simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were prepared. SGF (pH 2.0) was prepared by dissolving pepsin (3.2 g) and NaCl (2.0 g) in ultrapure water, adjusting the pH with concentrated HCl, and diluting to a final volume of 1.0 L. SIF (pH 6.8) was prepared by dissolving KH_2PO_4 (6.8 g) and trypsin (10.0 g) in ultrapure water, adding 77 mL of 0.2 M NaOH, and adjusting the pH with 0.1 M HCl. Both solutions were filtered through a 0.22- μm membrane to remove insoluble impurities.

The morphological changes of QUE@SP in these microenvironments were investigated using scanning electron microscopy (SEM). Briefly, QUE@SP (1 mg) was incubated in SGF (1.0 mL, pH 2.0) and SIF (1.0 mL, pH 6.8) sequentially at 37 °C with constant shaking at 200 rpm. At predetermined time points, the samples were collected and centrifuged at $2000 \times g$ for 5 min. The pellets were washed three times with phosphate-buffered saline (PBS), drop-cast onto silicon wafers, and lyophilized. Finally, the samples were sputter-coated with gold and examined via SEM (Gemini SEM 300, ZEISS, Germany).

2.6. Cell culture and cytotoxicity assays

The IEC-6 and RAW 264.7 cells (origins detailed in Section 4.1) were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% (v/v) penicillin-streptomycin. All cell cultures were maintained at 37 °C in a humidified atmosphere containing 5% CO_2 .

For cell viability assays, IEC-6 cells were seeded into 96-well plates at a density of 1×10^4 cells per well and pre-incubated in DMEM for 12 h. The culture medium was then replaced with fresh DMEM containing quercetin (QUE), SP, or QUE@SP at various concentrations (0, 6, 12, 25, 50, 100, and 200 $\mu\text{g}/\text{mL}$). After incubation for 24 h, the cells were washed three times with PBS. Cell viability was assessed using a standard cell counting kit-8 (CCK-8) assay (Beijing Biotopped Technology Co., Ltd., Beijing, China) according to the manufacturer's instructions. Cytotoxicity towards RAW 264.7 cells was evaluated using the identical protocol described above to determine the concentration-dependent effects of the formulations.

2.7. Live/dead staining assay under oxidative stress

To visualize cell viability under oxidative stress, IEC-6 cells were seeded in 24-well plates at a density of 5×10^4 cells/well and incubated in DMEM for 12 h. Subsequently, the cells were exposed to specific oxidative stress inducers in the presence or absence of QUE@SP (10 $\mu\text{g}/\text{mL}$) for 1 h. The induction systems included: (i) H_2O_2 (0.6 mM), (ii) Xanthine (140 μM) + Xanthine Oxidase (XO, 0.1 U/mL), and (iii) the Fenton reaction system consisting of H_2O_2 (0.6 mM) and FeSO_4 (2 μM). Following treatment, the culture medium was removed, and cells were gently rinsed with PBS. The cells were then stained using a Calcein AM/Propidium Iodide (PI) Double Staining Kit (Solarbio, Beijing, China) for 30 min. Finally, fluorescence images were captured using an EVOS fluorescence imaging system (Thermo Fisher Scientific, Waltham, MA, USA).

2.8. Intracellular ROS detection

IEC-6 cells were subjected to the oxidative stress induction protocols described in Section 4.7. To assess intracellular reactive oxygen species (ROS) levels, 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) was employed as a fluorescent probe. Non-fluorescent DCFH-DA permeates the cell membrane and is oxidized by intracellular ROS into highly fluorescent 2',7'-dichlorofluorescein (DCF). Briefly, after the indicated treatments, the cells were incubated with DCFH-DA (10 μM) for 30 min at 37 °C in the dark. Subsequently, the cells were washed three times with PBS to remove the excess probe, and fluorescence images were acquired using the EVOS fluorescence imaging system. The relative fluorescence intensities of DCF were subsequently quantified using

ImageJ software.

2.9. *In vitro* anti-inflammatory evaluation

RAW 264.7 cells were seeded into 12-well plates at a density of 5×10^4 cells per well and cultured in DMEM for 12 h. Subsequently, the cells were stimulated with lipopolysaccharide (LPS, 2 $\mu\text{g}/\text{mL}$) for 24 h to induce inflammation. After removing the medium and gently washing with PBS, the cells were treated with fresh medium containing QUE, SP, or QUE@SP (10 $\mu\text{g}/\text{mL}$) for another 24 h. Untreated RAW 264.7 cells served as the negative control.

Following treatment, the samples were prepared for both flow cytometry and immunofluorescence imaging. For flow cytometry, the cells were harvested into single-cell suspensions, while for imaging, the cells were processed *in situ*. Both sets of samples were fixed with 4% (w/v) paraformaldehyde (PFA) for 30 min and then blocked with blocking buffer (5% bovine serum albumin (BSA)) for 1 h at room temperature. The cells were subsequently incubated with primary antibodies against CD86 (an M1 marker; 1:200) and CD163 (an M2 marker; 1:200) at 4 °C overnight, followed by incubation with the corresponding fluorescent secondary antibodies (1:500) for 1 h at room temperature in the dark. Nuclei were counterstained with DAPI (1 $\mu\text{g}/\text{mL}$) for 5 min. Finally, quantitative analysis was performed using a flow cytometer (CytoFLEX, Beckman Coulter, USA), and morphological observation was conducted using the EVOS fluorescence imaging system.

2.10. *In vivo* evaluation in DSS-induced colitis model

Female C57BL/6 mice (6 weeks old, 18–20 g) were employed to establish the acute ulcerative colitis (UC) model. All animal care and experimental protocols were approved by the Institutional Animal Care and Use Committee of Northwestern Polytechnical University (Approval No. 202501035). Humane endpoints were strictly monitored; specifically, mice exhibiting a weight loss exceeding 20% of their initial body weight were euthanized to minimize suffering.

Mice were administered 3.5% (w/v) dextran sulfate sodium (DSS) dissolved in drinking water *ad libitum* for 7 consecutive days. To evaluate therapeutic efficacy, mice were randomly divided into five groups ($n = 5$ per group). The specific treatment regimen was as follows: (i) Control group: received sterile drinking water *ad libitum* and was administered ddH₂O via oral gavage once daily from day 2 to day 9; (ii) DSS model group: received 3.5% DSS water and was administered ddH₂O via oral gavage once daily from day 2 to day 9; (iii) treatment groups (SP, QUE, and QUE@SP): received 3.5% DSS water and were administered SP, QUE, or QUE@SP suspensions via oral gavage at a dose of 80 mg/kg once daily from day 2 to day 9.

During the experiment, body weight and disease activity index (DAI) scores (calculated based on weight loss, stool consistency, and rectal bleeding) were recorded daily. Following the 7-day DSS induction, all mice were maintained on regular water for a 2-day recovery period. On day 10, all mice were sacrificed.

Biocompatibility and histological analysis: Major organs (heart, liver, spleen, lung, and kidney) were harvested, weighed, and stained with hematoxylin and eosin (H&E) to evaluate the systemic toxicity of the treatments. Serum and colon tissues were collected for cytokine analysis and histopathological examination. For colonic assessment, the colon length was measured. Distal colon tissues were fixed, embedded in paraffin, and sectioned. Histological changes were examined using H&E and Alcian blue/periodic acid-Schiff (AB-PAS) staining. Immunofluorescence (IF) staining was performed using antibodies against ZO-1, occludin, CD86, and CD163. Immunohistochemistry (IHC) was conducted to detect MPO, TNF- α , and IL-6. Cytokine detection: Colon tissues were homogenized in PBS (pH 7.4) at a ratio of 1:9 (w/v). The levels of TNF- α and IL-6 in the homogenate supernatants were quantified using ELISA kits (Beijing Biotopped Technology Co., Ltd.) strictly following

the manufacturer's instructions.

Intestinal permeability assay: Intestinal permeability was assessed *in vivo* using FITC-dextran. Briefly, mice were fasted (deprived of food and water) for 12 h and then administered FITC-dextran (4 kDa, 500 mg/kg body weight) via oral gavage. Blood samples were collected 3 h post-administration, and the fluorescence intensity of FITC in the serum was measured to determine gut leakage.

2.11. 16S rRNA gene sequencing analysis of gut microbiota

Following euthanasia, fresh fecal samples were collected and immediately snap-frozen in liquid nitrogen. To analyze the gut microbiota composition, total genomic DNA was extracted from the fecal samples. The 16S rRNA gene amplicon libraries were constructed by amplifying the target hypervariable region (V3–V4) using specific primers. Subsequently, high-throughput sequencing was performed to profile the microbial community structure.

3. Results and discussion

3.1 Preparation and characterization of QUE@SP

Quercetin nanoparticles (QUEnano) were prepared via nanoprecipitation, encapsulating water-insoluble quercetin within a hydrophobic zein core stabilized by a cationic chitosan shell. SEM revealed a uniform spherical morphology (Fig. 2a), while DLS confirmed an average hydrodynamic diameter of 525.7 nm and a narrow PDI of 0.273 (Fig. 2b). This nanoencapsulation significantly enhanced the aqueous dispersibility of quercetin compared to its free form (Fig. 2c). The QUE@SP delivery system was constructed via electrostatic self-assembly between the cationic QUEnano and negatively charged SP. Successful loading was verified by a distinct shift in UV-Vis absorbance (Fig. 2d) and zeta potential reversal (Fig. 2g), where the initial negative surface charge of SP (-23.4 mV) inverted to +34.3 mV, consistent with the dense coating of cationic QUEnano (+51.1 mV). The assembly process exhibited rapid binding kinetics with equilibrium reached within 6 min, achieving a maximal loading efficiency of 93.39% at an optimal SP: QUEnano mass ratio of 2:1 (Figs. S1–S3).

To validate the system's theranostic potential and structural stability, fluorescence imaging was conducted. Bare SP exhibited characteristic blue-green coloration and strong intrinsic red autofluorescence (Cy5 channel) from chlorophyll, facilitating label-free *in vivo* gastrointestinal

tracking (Fig. 2e). Following assembly with FITC-labeled QUEnano, uniform green fluorescence decorated the microalgae surface *in vitro* (Fig. 2f). Crucially, live animal imaging of the QUE@SP group demonstrated precise *in vivo* co-localization of the green and red signals within the gut. This confirmed that the nanoparticles remained stably anchored to the carrier under complex physiological conditions. *In vitro* release profiles were evaluated to assess gastrointestinal transit performance (Fig. 2h). QUE@SP exhibited minimal premature release (8.37%) in simulated gastric fluid (SGF) over 1 h, demonstrating effective cargo protection against acidic digestion. This robust resistance is primarily attributed to the extremely hydrophobic nature of the inner zein core. Although the outer chitosan shell undergoes rapid protonation and swelling in the highly acidic SGF (pH 2.0), the dense zein matrix remains structurally intact, acting as an effective physical barrier that strictly confines the lipophilic quercetin and prevents massive premature leakage.

To rigorously evaluate the release kinetics in disease-relevant microenvironments, sequential release assays were conducted in SGF (1 h) followed by SIF supplemented with either a fresh murine fecal slurry (10% w/v) or H₂O₂ (1 mM). The comprehensive release profiles (Fig. 2h) demonstrated that drug release is significantly accelerated upon exposure to the colonic flora. The abundant microbiota-derived enzymes rapidly degrade the polysaccharide-protein matrix, achieving the highest cumulative release rate. Additionally, the localized inflammatory ROS environment (H₂O₂) also moderately facilitated the drug release compared to the standard SIF Control. This thoroughly confirms the stimuli-responsive, site-specific drug discharge capabilities of QUE@SP at the inflamed colon. This behavior was visually corroborated by longitudinal SEM imaging (Fig. 2i): as incubation progressed from 2 to 6 h, the initially dense layer of nanoparticles progressively degraded and detached from the microalgae scaffold, consistent with the sustained drug release profile. Furthermore, to validate the reliability of non-invasive *in vivo* tracking, the quantitative fluorescence stability of the microcarrier was evaluated. As shown in Figure S4, the relative fluorescence intensity of QUE@SP remained above 82% after 24 hours of sequential incubation in SGF and SIF, demonstrating robust resistance against signal quenching in gastrointestinal fluids.

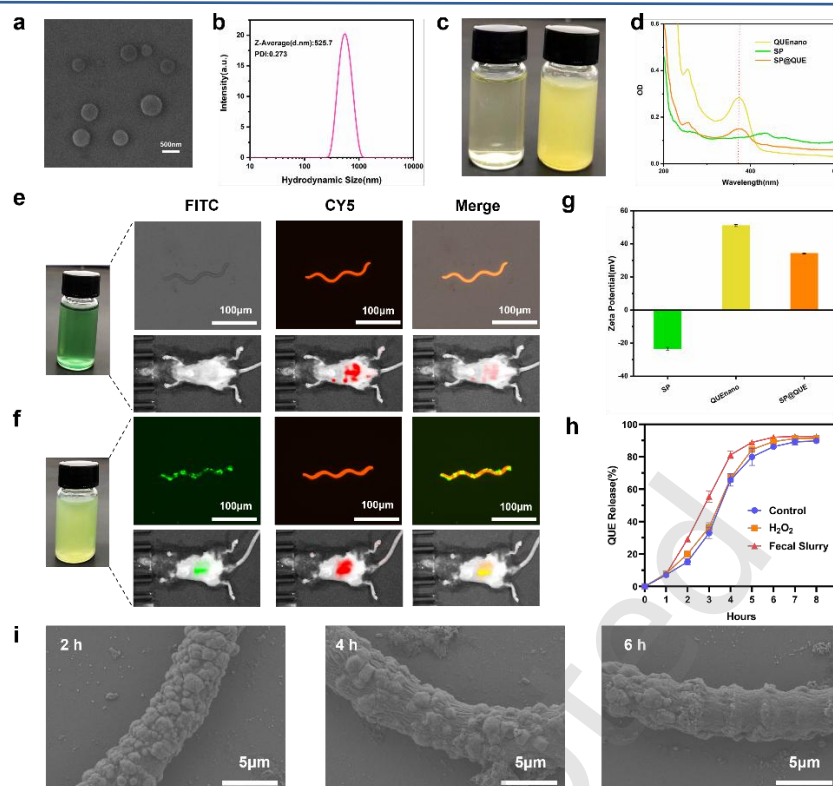


Figure 2 Fabrication and characterization of the microalgae-based drug carrier QUE@SP. (a) SEM image of the synthesized quercetin nanoparticles (QUEnano). (b) Particle size distribution of QUEnano. (c) Comparison of aqueous dispersibility between free quercetin (left) and QUEnano (right). (d) UV-Vis spectra of SP before and after QUEnano loading. (e) Bright-field and fluorescence images of bare SP. (f) Bright-field and fluorescence images of the assembled QUE@SP. (g) Zeta potentials of SP, QUEnano, and QUE@SP ($n=3$). (h) *In vitro* drug release profiles of QUE@SP during sequential incubation in SGF (0–1 h) and SIF (1–8 h) under different conditions: standard SIF (Control), SIF with 1 mM H_2O_2 , and SIF with 10% (w/v) fecal slurry ($n=3$). (i) Longitudinal SEM images of QUE@SP during drug release in SGF and SIF at 2 h, 4 h, and 6 h. Data are presented as mean $\pm$ SD.

3.2 *In vivo* spatiotemporal distribution and prolonged colonic retention of QUE@SP

The *in vivo* transit and anatomical distribution of the formulations were dynamically monitored using FITC-labeled nanoparticles. As shown in the longitudinal *in vivo* imaging (Figs. 3a, 3b), the control group (free NPs) exhibited rapid gastrointestinal clearance. Following oral administration, the fluorescence of free NPs peaked at 6 h but declined rapidly by 12 h, with negligible signals at 24 and 48 h. In contrast, QUE@SP exhibited a prolonged intestinal residence. Its fluorescence peaked at 12 h and remained strong in the abdominal region over the 48-h observation period, demonstrating an intensity approximately 4.6 times that of the control at 48 h.

Ex vivo imaging of the excised gastrointestinal tracts (Figs. 3c, 3d) corroborated these findings. At 12 h, free NPs were predominantly propelled to the distal colon and feces, confirming their rapid clearance via intestinal peristalsis. Conversely, QUE@SP accumulated densely throughout the ileum, cecum, and proximal colon, maintaining significantly higher fluorescence retention at 24 and 48 h.

These spatiotemporal distribution profiles confirmed that the helical *Spirulina* framework physically anchors within the intestinal villi. This shape-driven retention is strongly supported by recent pioneering studies, which utilized scanning electron microscopy (SEM) and frozen tissue sectioning to provide direct physical evidence of helical microalgae firmly trapped within intestinal villi, leading to significantly prolonged gastrointestinal transit times compared to spherical microalgae[48, 49]. In alignment with these established micro-morphological proofs, this distinct “hydrodynamic locking” transforms the transient transit of nanoparticles into a sustained mucosal depot for microbiota-triggered drug release at the inflamed epithelium. Clinically, unlike conventional spherical carriers that are prone to rapid washout during colitis-associated diarrhea, this shape-driven 48-hour retention theoretically reduces the required dosing frequency from multiple daily doses to once every two days. By maintaining a prolonged local therapeutic window, this platform holds immense practical value for mitigating systemic toxicity and improving patient compliance in chronic IBD management.

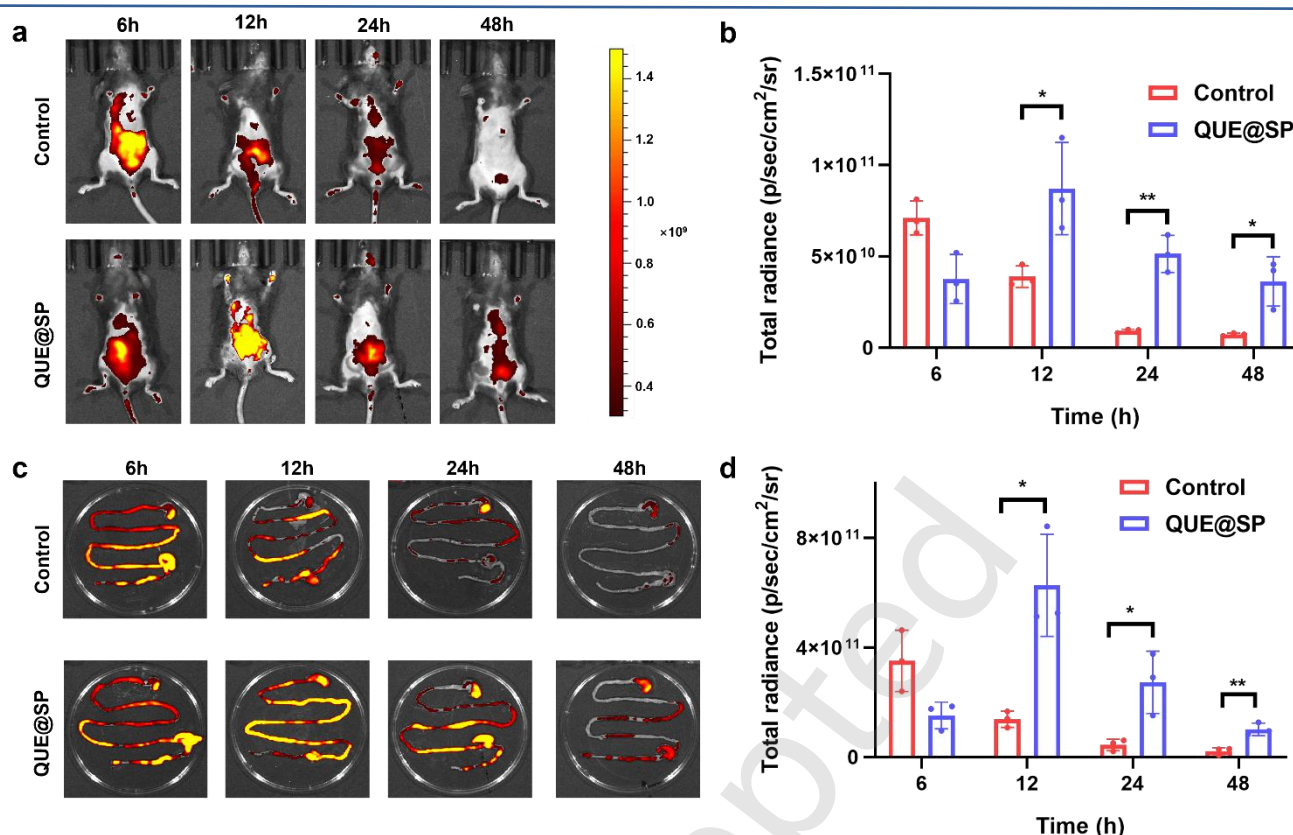


Figure 3 *In vivo* and ex vivo spatiotemporal distribution and prolonged intestinal retention of QUE@SP. (a, b) Qualitative *in vivo* fluorescence imaging (a) and the corresponding quantitative analysis of fluorescence intensity (b) of mice orally administered with free NPs (Control) or QUE@SP at predefined time points (4, 12, 24, and 48 h). (c, d) Qualitative ex vivo imaging of the excised gastrointestinal tracts (c) and the corresponding quantitative analysis of intestinal fluorescence retention (d) at the respective time points. Data are presented as mean $\pm$ SD ($n = 3$; * $P < 0.05$, ** $P < 0.01$).

3.3 QUE@SP alleviates intracellular oxidative stress via its multi-enzyme mimicking activities

The CCK-8 assay was employed to assess the cytotoxicity of SP, QUE, and QUE@SP on IEC-6 cells. After a 24-h incubation with materials at concentrations up to 200 $\mu\text{g/mL}$, all groups exhibited high cell viability, confirming their excellent biocompatibility (Fig. 4a and Fig. S5). To investigate the enzyme-mimetic antioxidant properties of QUE@SP, three typical reactive oxygen species (ROS)—superoxide anion ($\text{O}_2^{\bullet-}$), hydroxyl radical ($\bullet\text{OH}$), and hydrogen peroxide (H_2O_2)—were selected to evaluate the superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) mimicking activities of the material, respectively. When H_2O_2 was used to induce oxidative cell damage, increasing its concentration from 0.2 mM to 0.8 mM reduced cell viability from 93.66% to 63.89%, respectively. However, after co-incubation with QUE@SP, the oxidative stress level in cells was significantly alleviated, restoring cell viability to 97.29% and 72.28% under the respective H_2O_2 concentrations (Fig. 4b). To simulate high-intensity oxidative stress mediated by $\text{O}_2^{\bullet-}$, xanthine oxidase (XO, 0.1 U) and xanthine were added to the culture medium. At xanthine concentrations of 100 μM and 160 μM , the viability of IEC-6 cells decreased to 94.85% and 62.64%, respectively, due to $\text{O}_2^{\bullet-}$ -induced oxidative damage. Following co-incubation with QUE@SP, the intracellular oxidative stress was mitigated, effectively restoring cell viability to 96.01% and 71.81% under the same conditions (Fig. 4c). To verify the GPx-like antioxidant characteristic of QUE@SP, $\bullet\text{OH}$ was generated in the medium by combining FeSO_4 (2 μM) with varying concentrations of H_2O_2 . Owing to the strong oxidative effect of $\bullet\text{OH}$, cell viability declined markedly; at H_2O_2 concentrations of 0.2 mM and 0.8 mM, cell viability dropped to 84.51% and 50.12%, respectively. In the presence of QUE@SP, however, cytotoxicity was markedly

reduced, and cell viability was elevated to 90.14% and 63.44%, respectively (Fig. 4d). To visually assess cell survival, Calcein AM/PI double staining was employed. Severe ROS environments were generated by treating IEC-6 cells with H_2O_2 (0.6 mM), XO (0.1 U) + xanthine (140 μM), or FeSO_4 (2 μM) + H_2O_2 (0.6 mM). Cells subjected to these ROS treatments exhibited markedly stronger red fluorescence (indicating dead cells) compared with normally cultured cells. However, after co-incubation with QUE@SP, the intracellular oxidative stress was alleviated, and the proportion of green fluorescence (representing live cells) increased substantially, demonstrating the potent antioxidant capacity of QUE@SP (Fig. 4e).

Intracellular oxidative stress was further quantified using the fluorescent probe DCFH-DA. Cells were exposed to H_2O_2 (0.6 mM), xanthine/xanthine oxidase (140 μM /0.1 U), or FeSO_4 / H_2O_2 (2 μM /0.6 mM) to generate specific oxidative damage. Relative to normal controls, the three treatments raised the percentage of DCF-positive cells by 91.95%, 108.67%, and 133.41%, respectively. QUE@SP intervention significantly suppressed these proportions by 61.1%, 83.79%, and 85.01%, respectively (Figs. 4f–4i). These variations in oxidative stress were further corroborated by quantitative flow cytometry analysis (Fig. S6). Following exposure to the three oxidative environments, the fluorescence peaks exhibited a distinct rightward shift, reflecting severe intracellular ROS accumulation. Conversely, co-incubation with QUE@SP effectively induced a leftward shift back toward the baseline, providing precise quantitative evidence that aligns with the imaging results. Fluorescence microscopy further verified this excellent ROS-scavenging performance of QUE@SP (Fig. 4j). The substantial reduction in positive cells indicates that QUE@SP effectively scavenges intracellular ROS and mitigates oxidative stress in the intestinal epithelium.

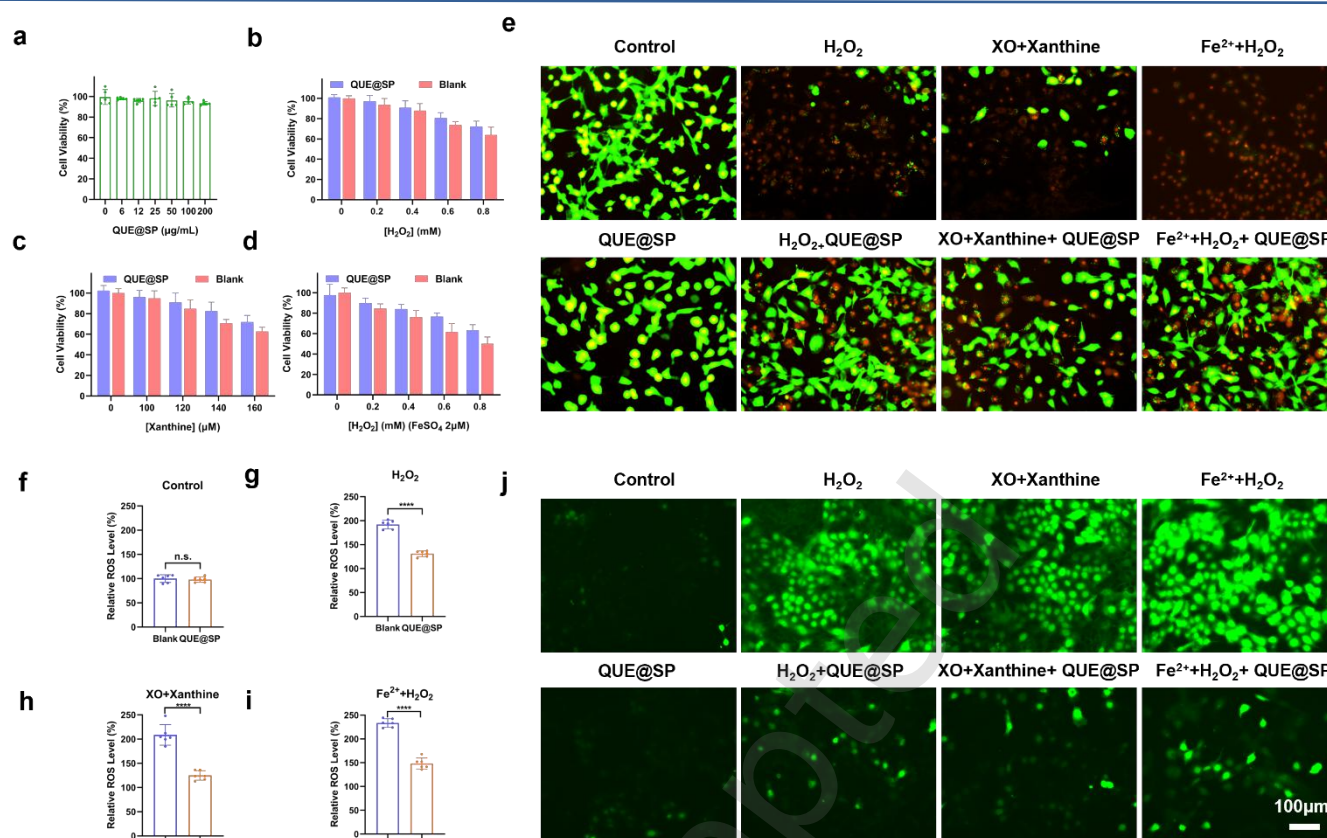


Figure 4 Alleviation of intracellular oxidative stress via the multi-enzyme mimicking antioxidant activities of QUE@SP. (a) Viability of IEC-6 cells incubated with QUE@SP at varying concentrations (0–200 μg/mL) for 24 h (n=5). (b) Viability of IEC-6 cells treated with H₂O₂ (0.2–0.8 mM) in the presence or absence of QUE@SP (n=6). (c) Viability of IEC-6 cells treated with xanthine oxidase (XO, 0.1 U) and xanthine (0–160 μM) with or without QUE@SP (n=6). (d) Viability of IEC-6 cells treated with FeSO₄ (2 μM) and H₂O₂ (0.2–0.8 mM) with or without QUE@SP (n=6). (e) Representative fluorescence microscope images of IEC-6 cells stained with Calcein-AM (live) and PI (dead) under different treatments: Control, QUE@SP, H₂O₂ (0.6 mM), XO (0.1 U) + xanthine (140 μM), FeSO₄ (2 μM) + H₂O₂ (0.6 mM), and corresponding groups co-incubated with QUE@SP. (f–i) Quantitative ImageJ analysis of relative DCF fluorescence intensities in IEC-6 cells treated with H₂O₂ (f, g), XO + XA (h), and FeSO₄ + H₂O₂ (i) with or without QUE@SP (n=6). (j) Fluorescence images of IEC-6 cells stained with the DCFH-DA probe to visualize intracellular ROS scavenging under different treatments (Control, QUE@SP, H₂O₂, XO + Xanthine, FeSO₄ + H₂O₂, H₂O₂ + QUE@SP, XO + Xanthine + QUE@SP and FeSO₄ + H₂O₂ + QUE@SP). Data are presented as mean ± SD (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, and n.s. P > 0.05).

3.4 Anti-inflammatory activity of QUE@SP in cells

The cytotoxicity of SP, QUE, and QUE@SP was evaluated *In vitro* using murine monocyte-macrophage leukemia cells (RAW 264.7). After a 24-h co-incubation with the materials at concentrations ranging from 0 to 200 μg/mL, cell viability was assessed using a CCK-8 assay. The results indicated that all three materials exhibited excellent biocompatibility, with cells in all groups maintaining high viability (Fig. S7). Upon inflammatory stimulation, macrophages become activated and trigger an inflammatory cascade. In this study, murine macrophage RAW 264.7 cells were treated with lipopolysaccharide (LPS), a potent pro-inflammatory agent, to induce intracellular inflammatory responses. The experimental groups included pretreatment with QUE@SP, QUE, or SP, along with positive (LPS only) and negative (untreated) controls. Macrophage phenotypes were assessed via immunofluorescence staining for CD86 (pro-inflammatory M1 marker) and CD163 (anti-inflammatory M2 marker). Quantitative ImageJ analysis revealed that LPS treatment increased the relative fluorescence intensity (RFI) of the M1 marker CD86 to 1.53 times that of the control

group. Upon treatment with QUE@SP, however, the intracellular inflammatory level was significantly reduced, as indicated by a decrease in CD86 RFI to 1.20 times that of the control. This downregulation demonstrated that QUE@SP effectively inhibited pro-inflammatory macrophage activation (Fig. 5a, Fig. S8a). Quantitative flow cytometry analysis of the M1 marker further corroborated this reduction in the inflammatory response (Fig. 5b). Conversely, LPS stimulation markedly reduced the fluorescence intensity of the M2 macrophage marker CD163. Quantitative analysis showed that the RFI of CD163 in the LPS group decreased to 37.12% of the control level. Following treatment with QUE@SP, the RFI of CD163 recovered significantly to 88.27% of the control level, indicating that the material effectively promoted an anti-inflammatory response (Figs. 5c, 5d, Fig. S8b). Collectively, the immunofluorescence and flow cytometry data demonstrated that QUE@SP efficiently alleviates intracellular inflammation and remodels macrophage polarization.

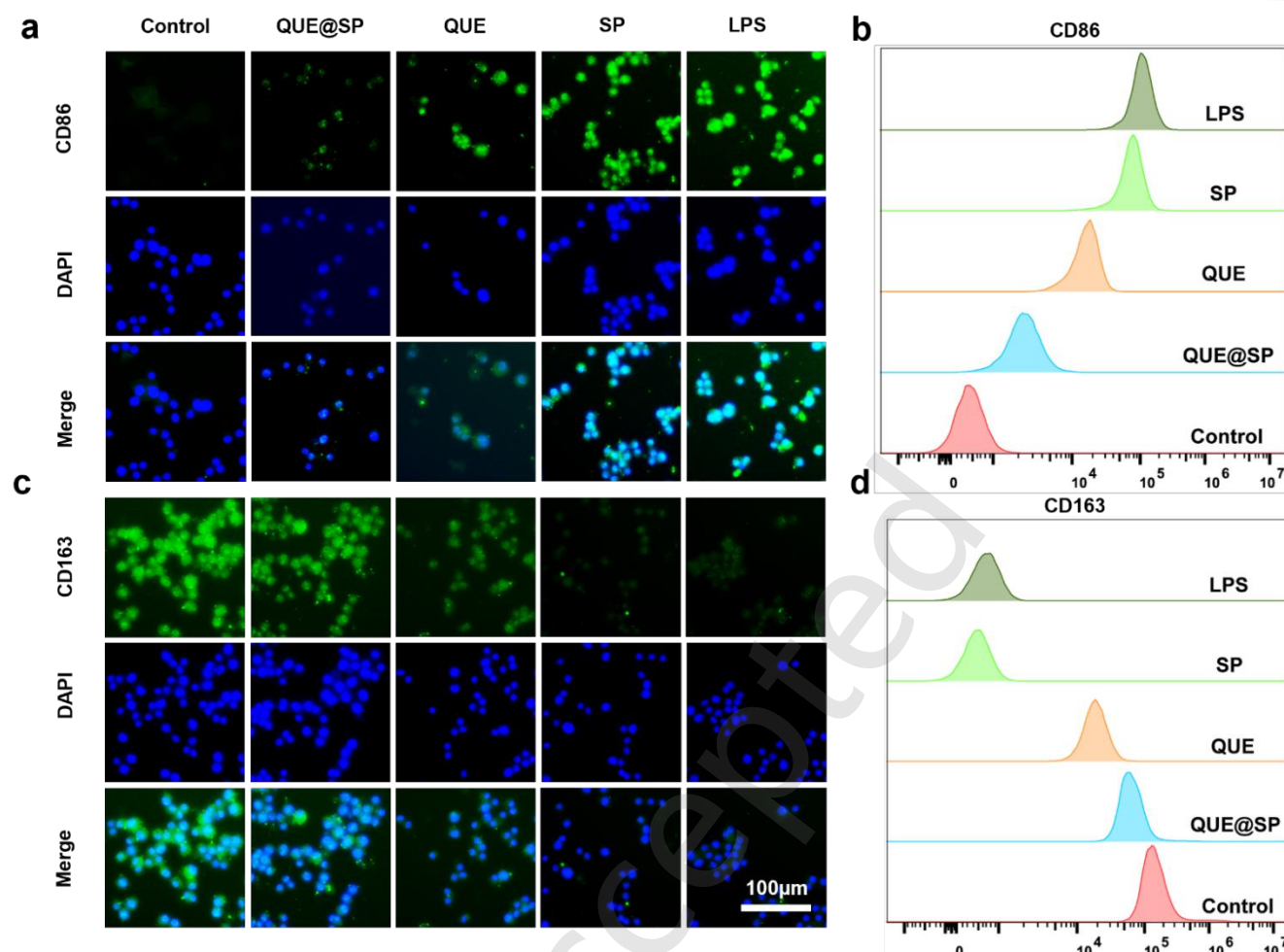


Figure 5 Remodeling of macrophage polarization and alleviation of cellular inflammation by QUE@SP. (a, b) Representative immunofluorescence analysis (a) and quantitative flow cytometry analysis (b) of the pro-inflammatory M1 marker CD86 in LPS-stimulated RAW 264.7 macrophages following treatment with SP, QUE, or QUE@SP. (c, d) Representative immunofluorescence analysis (c) and quantitative flow cytometry analysis (d) of the anti-inflammatory M2 marker CD163 under the same treatment conditions.

3.5. *In vivo* therapeutic efficacy of QUE@SP in DSS- induced ulcerative colitis mice

Based on the favorable biocompatibility, excellent ROS-scavenging capacity, and anti-inflammatory activity described above, the oral therapeutic efficacy of QUE@SP was evaluated in a mouse model of acute ulcerative colitis induced by dextran sulfate sodium (DSS). Acute colitis was induced by administering 3.5% DSS in drinking water for 7 days (Fig. 6a). To protect mice from colitis and evaluate the therapeutic effect of QUE@SP, the mice were orally administered SP, QUE, or QUE@SP once daily from day 2 to day 9. Mice in the DSS group received an equal volume of ddH₂O. As shown, mice without DSS induction remained normal with stable body weight, whereas mice in the DSS group exhibited severe weight loss and clinical symptoms including diarrhea and bloody stools due to DSS-induced injury. The body weight retention rates in the DSS, SP, QUE, and QUE@SP groups decreased to 82.74%, 82.41%, 85.89%, and 88.73% of baseline, respectively. The disease activity index (DAI) was calculated as the average of the fecal

consistency index, fecal bleeding index, and weight loss index (Table S1). DAI was highest in the DSS group (3.8), and decreased to 3.53, 2.53, and 1.13 in the SP, QUE, and QUE@SP groups after respective treatments. Notably, QUE@SP treatment achieved an approximately 70.3% reduction in DAI compared to the untreated DSS group, demonstrating its pronounced therapeutic efficacy. (Figs. 6b–6e). To visually reflect the severity of colitis, colon length was measured, showing significant shortening after DSS induction (Figs. 6f, 6h). The average colon lengths in the Control, DSS, SP, QUE, and QUE@SP groups were 7.01 cm, 4.78 cm, 4.68 cm, 6.05 cm, and 6.76 cm, respectively, indicating a gradual alleviation of colonic damage. Furthermore, DSS-induced injury led to varying degrees of splenomegaly in mice, with greater inflammation corresponding to larger spleen size (Fig. 6g). The spleen index, which assesses spleen weight relative to body weight, was significantly lower in the QUE@SP group compared with the DSS group, further confirming the effective mitigation of systemic inflammation associated with colitis (Fig. 6i).

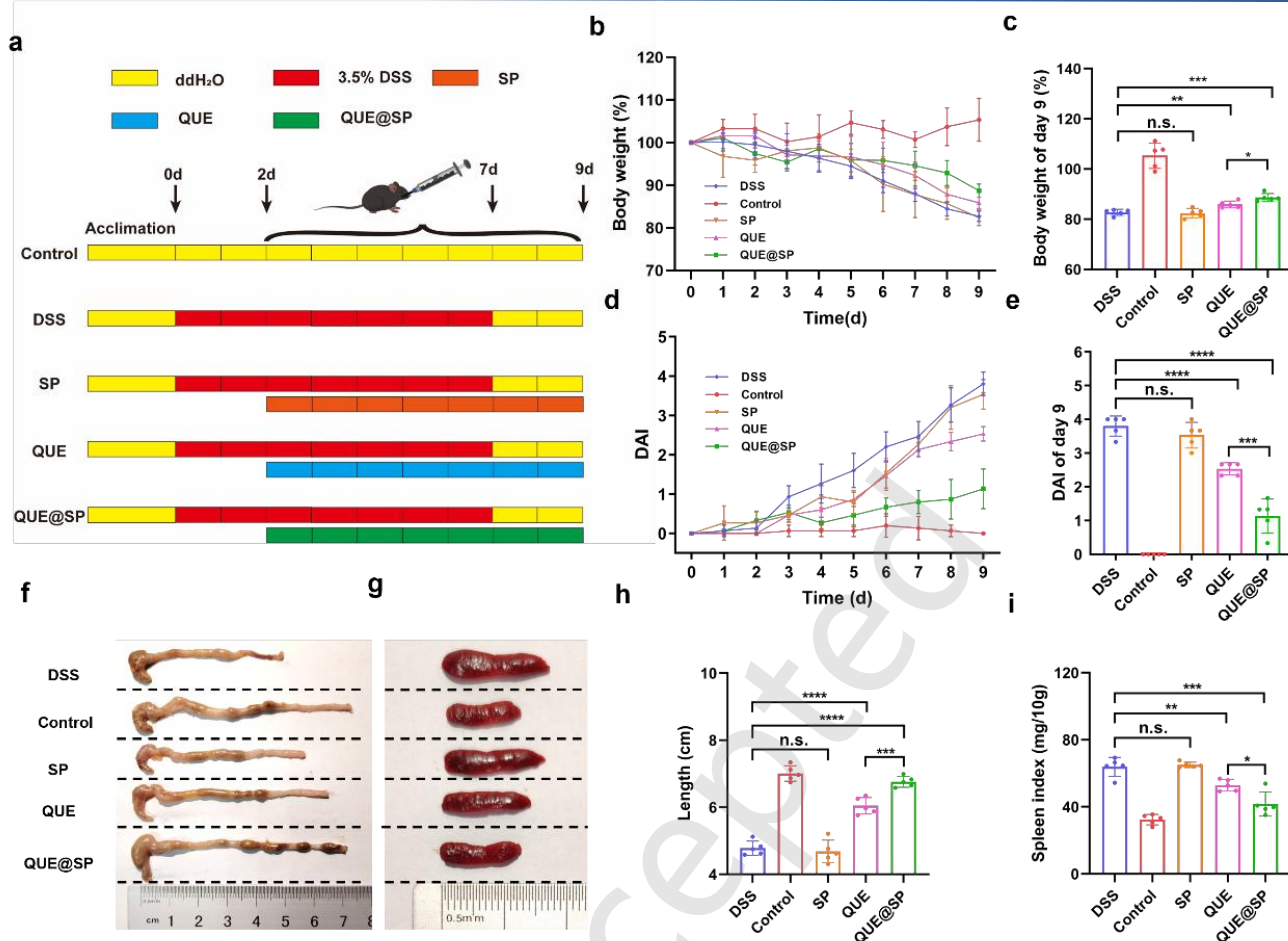


Figure 6 Alleviation of DSS-induced colitis in mice by QUE@SP. (a) Schematic illustration of the *in vivo* experimental design. (b, c) Normalized body weight changes during the treatment period (b) and at the experimental endpoint on day 9 (c). (d, e) Disease activity index (DAI) scores during the treatment period (d) and on day 9 (e). (f, g) Representative macroscopic images of the excised colons (f) and spleens (g). (h) Quantitative analysis of colon lengths. (i) Spleen indices (spleen-to-body weight ratio, mg/10 g). Data are presented as mean $\pm$ SD ($n = 5$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, and n.s. $P > 0.05$).

On day 10, blood and colon samples were collected from the mice for histopathological evaluation (H&E and AB/PAS staining), immunohistochemistry (IHC), and inflammatory cytokine detection. H&E staining of colon sections from the DSS group revealed typical ulcerative colitis histopathological features, including focal mucosal ulceration, extensive crypt loss, goblet cell depletion, and substantial inflammatory cell infiltration. Histological scores were used to quantitatively assess colon tissue damage across the groups (Table S2). The SP group exhibited histological scores similar to those of the DSS group, indicating that Spirulina alone had no significant therapeutic effect. Mice in the QUE group showed mild symptom alleviation, whereas the QUE@SP group demonstrated pronounced therapeutic efficacy compared to the DSS, SP, and QUE groups. Specifically, the histological score in the QUE@SP group decreased to 5.6, compared to 16.0 in the DSS group, with essentially normal mucosal architecture, regularly arranged tubular crypts, an increased goblet cell proportion, and reduced inflammatory cell infiltration (Figs. 7a, 7f). Similarly, AB-PAS staining was performed to evaluate intestinal health by assessing acidic mucin secretion on the intestinal surface. Staining results showed that the QUE@SP group (65.86% positive area) exhibited a significantly larger positive area compared to the DSS (12.69%), SP (12.63%),

and QUE (29.83%) groups, further confirming its therapeutic effect on colitis (Figs. 7b, 7g). Moreover, immunohistochemical staining was used to assess myeloperoxidase (MPO) expression, a marker that reflect neutrophil infiltration in colon tissue. As shown in Fig. 7c and Fig. 7h, MPO levels in the QUE@SP group were markedly lower than in all other treatment groups, demonstrating the potent anti-inflammatory effect of QUE@SP. Inflammatory cytokines in colon tissue were measured using enzyme-linked immunosorbent assays (ELISA), and the expression of inflammatory factors in intestinal cells was observed via immunohistochemical staining. The results indicated that QUE@SP treatment restored intestinal homeostasis and reduced the levels of the pro-inflammatory cytokines IL-6 and TNF- α (Figs. 7d, 7e, 7i and 7j). Additionally, the biocompatibility of SP, QUE, and QUE@SP *in vivo* was evaluated. After H&E staining of heart, liver, spleen, lung, and kidney sections from all five groups of samples, including the Control and DSS groups, no significant pathological damage was observed, confirming the excellent biosafety and biocompatibility of SP, QUE, and QUE@SP (Fig. S9). In summary, QUE@SP alleviated oxidative stress and reduced intestinal inflammation in mice with DSS-induced acute colitis.

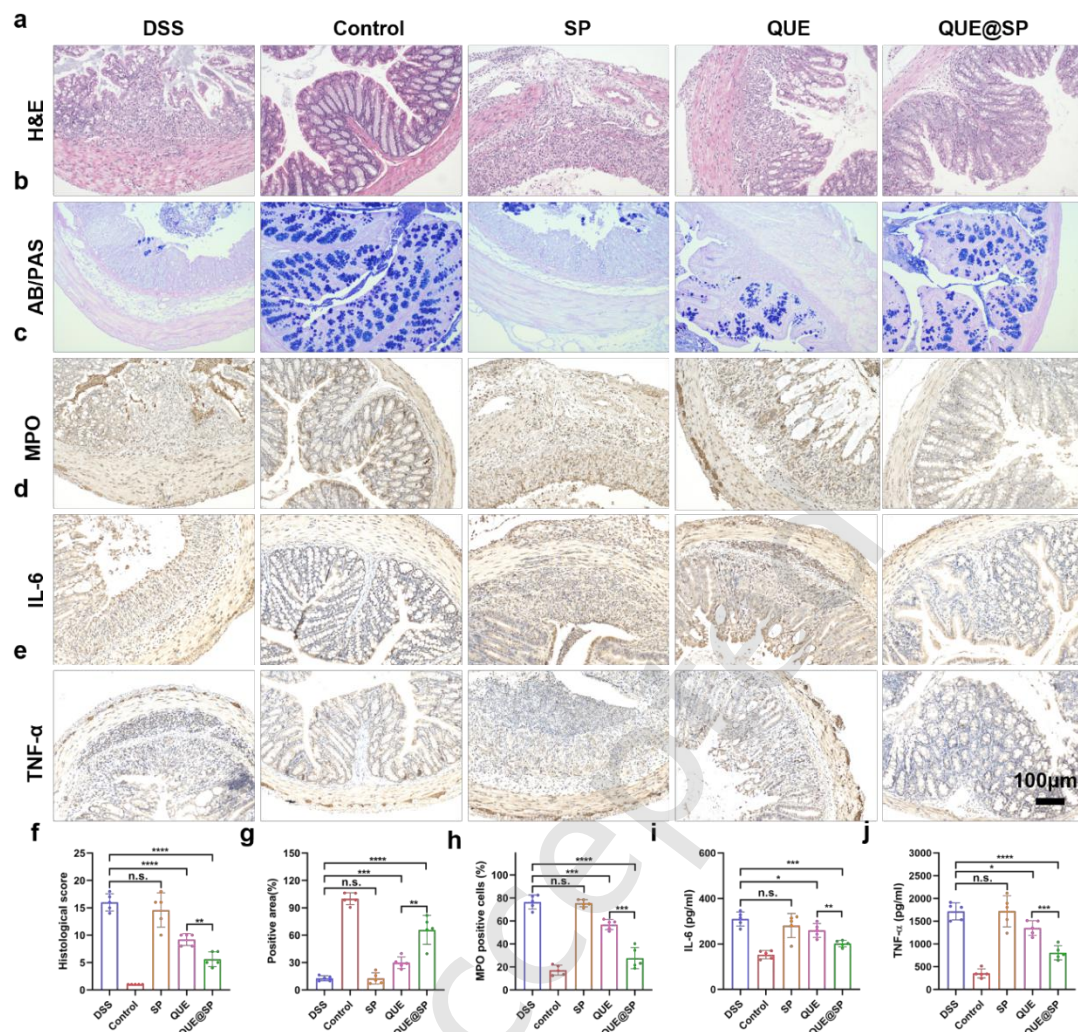


Figure 7 *In vivo* enhanced therapeutic efficacy of QUE@SP against DSS-induced acute colitis in mice. (a) Representative images of H&E staining of colon tissues. (b) Representative images of AB-PAS staining of colon tissues. (c) Immunohistochemical staining of MPO-positive cells in colon tissues. (d, e) Immunohistochemical staining of IL-6 (d) and TNF- α (e)-positive cells in colon tissues. (f) Histological scores. (g) Quantification of the AB-PAS-positive area. (h) Quantification of MPO-positive cells. (i, j) Quantitative ELISA analysis of IL-6 (i) and TNF- α (j) levels in colon tissues. Data are presented as mean $\pm$ SD (n = 5, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, and n.s. P > 0.05).

Immunofluorescence (IF) analysis was employed to investigate the structural remodeling of the intestinal epithelium and alterations in immune cell phenotypes. Occludin and Zonula Occludens-1 (ZO-1) serve as critical markers for tight junction (TJ) integrity. In the DSS-induced colitis group, the expression of these proteins was significantly downregulated, indicating severe damage to the colonic mucosa. Previous studies have established that excessive ROS compromise the integrity of TJ proteins and the epithelial barrier. Following treatment with QUE@SP, excessive ROS at the inflammatory sites were effectively scavenged, facilitating the restoration of the intestinal barrier (Figs 8a, 8b). Specifically, quantitative analysis revealed that the expression levels of Occludin and ZO-1 increased by 12.37% and 11.67%, respectively, compared to the DSS group (Figs 8e, 8f). To functionally validate this structural recovery, colonic permeability was evaluated using an *in vivo* FITC-dextran assay. Consistent with the IF results, the level of FITC-dextran in the serum was markedly decreased following QUE@SP treatment compared with the other interventions (Fig. S10). Collectively, this structural upregulation of TJ proteins and the consequent functional reduction in mucosal permeability are crucial for preventing the translocation of luminal bacteria and antigens into the lamina propria, thereby averting aberrant mucosal immune

responses.

Furthermore, IF staining for CD86 and CD163 was performed to characterize macrophage polarization and elucidate the role of macrophages in the inflammatory microenvironment. As shown in Fig. 8c, the DSS group exhibited significantly higher fluorescence intensity for CD86, indicating that the inflammatory environment promotes the infiltration and proliferation of pro-inflammatory M1 macrophages. Conversely, QUE@SP treatment markedly attenuated this response, resulting in a 31.26% decrease in the M1 macrophage population compared to the DSS group (Fig. 8g). Regarding the anti-inflammatory M2 phenotype (CD163+), the DSS group displayed the lowest fluorescence intensity among all cohorts, reflecting a severely compromised anti-inflammatory state (Fig. 8d). However, QUE@SP treatment successfully reversed this trend, enhancing the anti-inflammatory milieu and increasing the M2 macrophage population by 11.34% (Fig. 8h). Collectively, these findings demonstrate that QUE@SP modulates the intestinal immune microenvironment by shifting macrophage polarization from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype, thereby effectively alleviating intestinal inflammation.

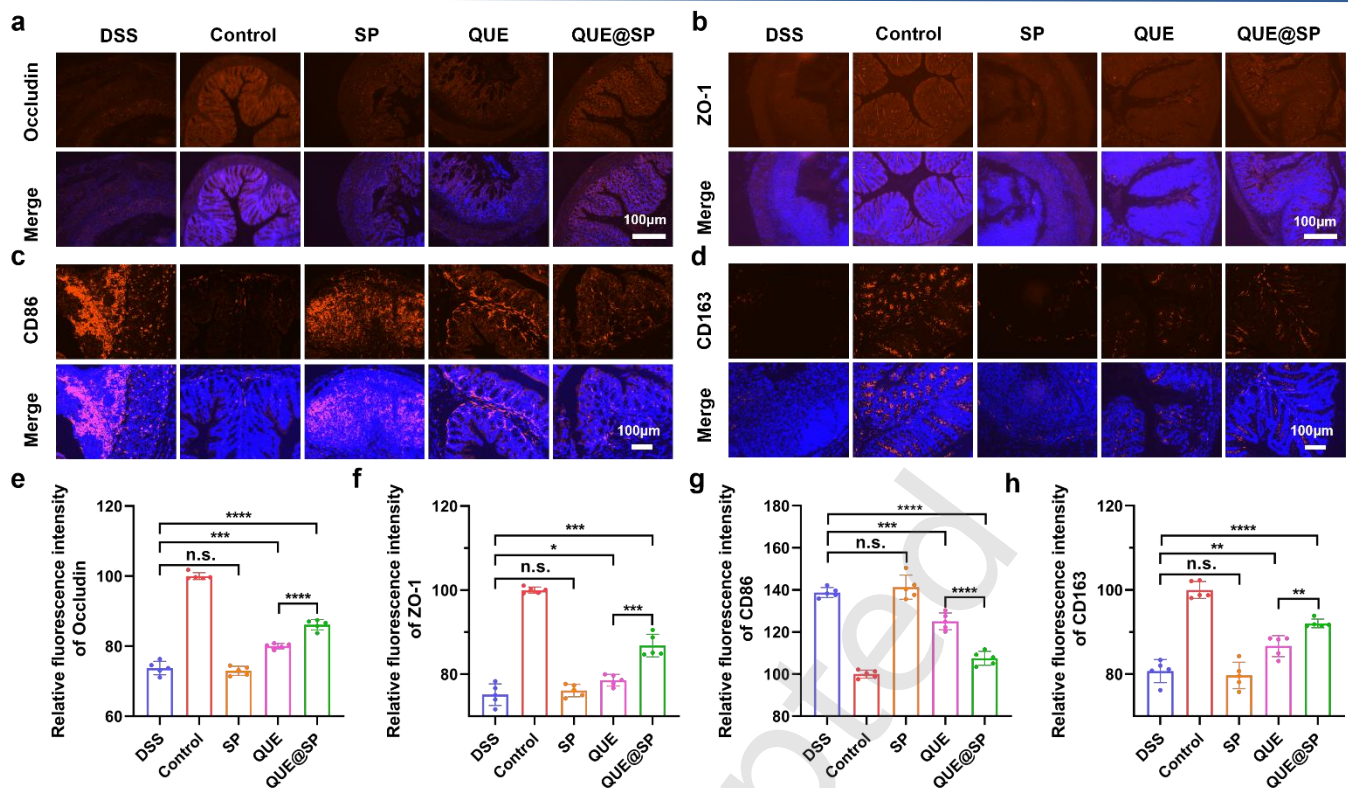


Figure 8 Evaluation of intestinal barrier integrity and macrophage polarization in mice. (a, b) Representative immunofluorescence images of the tight junction proteins Occludin (a) and ZO-1 (b) in colon tissues. (c, d) Representative immunofluorescence images of the macrophage polarization markers CD86 (c, M1 macrophages) and CD163 (d, M2 macrophages). (e, f) Quantitative analysis of the relative fluorescence intensities of Occludin (e) and ZO-1 (f). (g, h) Quantification of the expression levels of CD86 (g) and CD163 (h). Nuclei were stained with DAPI (blue). Data are presented as mean $\pm$ SD ($n = 5$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, and n.s. $P > 0.05$).

3.6. Modulation of Gut Microbiota Composition by QUE@SP Treatment

To evaluate the therapeutic impact of QUE@SP on the gut microbiome in colitis, 16S rRNA gene sequencing (V3–V4 region) was performed on fecal samples from mice in each group. Alpha diversity indices, including ACE, Chao1, Shannon, and observed OTUs, were employed to characterize the ecological diversity within each group (Figs. 9a–9c and Fig. S11). The results demonstrated that QUE@SP treatment significantly enhanced gut microbiota diversity compared to the DSS group. The rank-abundance curve, a standard method for visualizing species diversity, reflects species richness through the horizontal span of the curve. As shown in Fig. 9d, the QUE@SP group exhibited a much broader span than the DSS group, indicating a substantial recovery in species richness. Regarding Beta diversity, both principal coordinate analysis (PCoA) and non-metric multidimensional scaling (NMDS) revealed distinct clustering patterns, distinguishing the DSS group from the control group. Notably, among all colitis-affected groups, the QUE@SP group clustered most closely with the Control group (Figs. 9e, 9f). This suggests that the effective scavenging of excessive ROS and the subsequent alleviation of oxidative stress by QUE@SP facilitated the restoration of the microbial community composition to a state resembling that of healthy mice. Additionally, Venn diagram analysis indicated that the number of species in the QUE@SP group was closest to that of the control group, further confirming the recovery of bacterial richness (Fig. 9g). LEfSe cladogram analysis further confirmed that the phylogenetic structure of the microbiota in the QUE@SP group was significantly restored compared to the DSS group (Fig. 9h). Detailed taxonomic analysis was conducted at the family and genus levels. At the family level, the relative abundance of

Ruminococcaceae in the QUE@SP group was restored to levels comparable to those of the healthy control group. These beneficial bacteria are pivotal for fermenting dietary fiber into short-chain fatty acids (SCFAs). SCFAs are critical bacterial metabolites that maintain immune homeostasis and alleviate intestinal inflammation (Figs. 9i–9k). At the genus level, QUE@SP treatment significantly increased the relative abundance of Akkermansia, a mucin-degrading bacterium known to enhance intestinal barrier function and reduce inflammatory responses. Conversely, the population of Escherichia-Shigella, an IBD-associated pathobiont, was notably suppressed following QUE@SP treatment. Since Escherichia-Shigella can breach the epithelial barrier and induce macrophage apoptosis—thereby exacerbating colitis—its suppression is conducive to restoring intestinal homeostasis and resolving inflammation (Fig. S12 and Figs. 9l, 9m). Collectively, these findings elucidate a stepwise therapeutic mechanism for the QUE@SP platform. The process begins with shape-driven hydrodynamic locking, which ensures localized carrier accumulation at the inflamed colon. Microbiota-responsive degradation then triggers the precise release of quercetin to efficiently neutralize excessive ROS. The reduction in oxidative stress protects tight junction proteins from degradation and promotes mucosal barrier repair, effectively restricting the continuous infiltration of luminal pathobionts. Coupled with the direct immunomodulatory activity of quercetin, this restored barrier integrity drives the mucosal microenvironment to shift from a pro-inflammatory M1 phenotype to a pro-healing M2 state. Ultimately, this multifaceted pathway interrupts the pathogenic loop of immune overactivation and mucosal injury, leading to the resolution of intestinal inflammation and the alleviation of colitis symptoms.

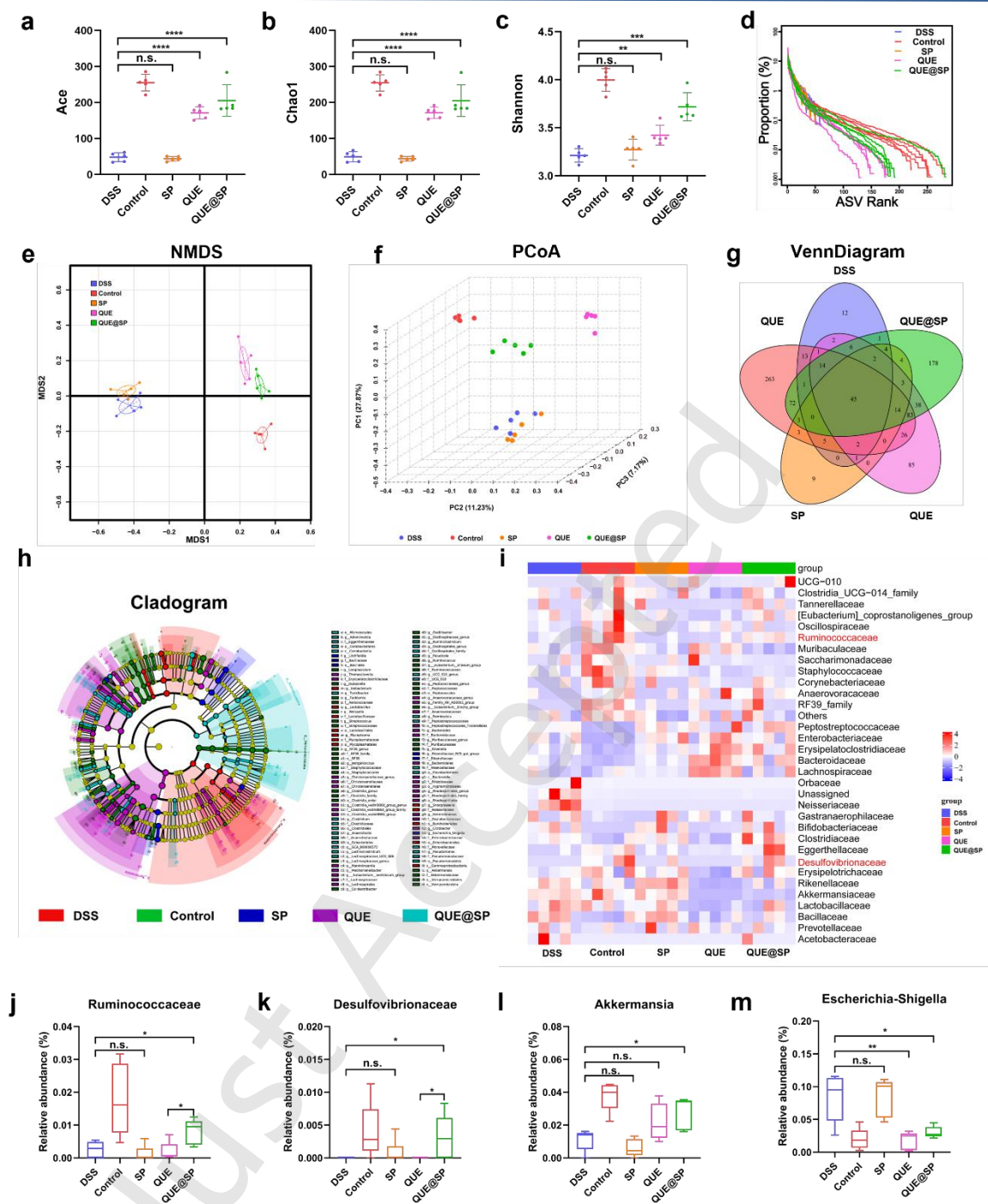


Figure 9 Modulation of gut microbiota composition by QUE@SP treatment in mice with DSS-induced colitis. (a–c) Alpha diversity indices, including ACE (a), Chao1 (b), and Shannon (c). (d) Rank-abundance curves of the microbial communities. (e, f) Beta diversity evaluated via a 2D non-metric multidimensional scaling (NMDS) plot (e) and a 3D principal coordinate analysis (PCoA) plot (f). (g) Venn diagram illustrating shared and unique ASVs. (h) LEfSe cladogram of the phylogenetic distribution and specific taxonomic biomarkers. (i) Heatmap of the relative abundances of the gut microbiota at the family level. (j–m) Relative abundances of Ruminococcaceae (j), Desulfovibrionaceae (k), Akkermansia (l), and Escherichia-Shigella (m). Data are presented as mean $\pm$ SD ($n = 5$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, and n.s. $P > 0.05$)

4 Conclusions

In summary, we engineered a bio-inspired theranostic platform (QUE@SP) by electrostatically anchoring cationic, quercetin-loaded zein/chitosan nanoparticles onto the surface of *Spirulina platensis*. This hierarchical design effectively addressed the poor aqueous solubility and presystemic clearance of the hydrophobic cargo. Crucially, the biomimetic helical morphology of the microcarrier induced a hydrodynamic locking effect within the intestinal villi. By successfully resisting the gastrointestinal washout effect, this spatial anchoring established a sustained mucosal depot for microbiota-triggered, site-specific drug release.

Consequently, this spatiotemporal synchronization maximized localized drug exposure, translating into potent and multifaceted therapeutic efficacy against murine colitis. Furthermore, as an inherently biocompatible carrier, SP facilitated self-trackable monitoring of mucosal distribution via its highly stable intrinsic fluorescence, followed by complete biodegradation and nutritional absorption. Collectively, this study establishes a bio-inspired, shape-driven paradigm that repurposes natural microalgae into a precision oral vehicle, providing a comprehensive, clinically translatable, and biologically integrated strategy for targeted colitis therapy.

Electronic Supplementary Material: Supplementary material (Figs. S1–S12) is available in the online version of this article.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Statistical Analysis

All quantitative data are expressed as the mean $\pm$ standard deviation (SD). Statistical analyses were performed using GraphPad Prism software (Version 9.0). Comparisons between two independent groups were evaluated using the unpaired Student's t-test. For comparisons involving multiple groups, a One-way Analysis of Variance (ANOVA) followed by Tukey's post-hoc test was utilized. Differences were considered statistically significant at $P < 0.05$ (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

Declaration of competing interest

All the contributing authors reports no conflict of interests in this work.

Author contribution statement

K. L.: Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **W. H. Z.:** Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **J. H. L.:** Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **J. R. W.:** Methodology, Investigation, Formal analysis, Data curation. **L. F. Y.:** Formal analysis, Data curation. **J. X. L.:** Methodology, Investigation, Formal analysis, Data curation. **J. W. H.:** Methodology, Investigation, Formal analysis. **P. L. (Peng Li):** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. **P. L. (Peng Lin):** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Use of AI statement

None.

References

- [1] Ng, S. C.; Shi, H. Y.; Hamidi, N.; Underwood, F. E.; Tang, W.; Benchimol, E. I.; Panaccione, R.; Ghosh, S.; Wu, J. C. Y.; Chan, F. K. L.; Sung, J. J. Y.; Kaplan, G. G. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet* **2017**, *390*, 2769–2778.
- [2] Kaplan, G. G. The global burden of IBD: from 2015 to 2025. *Nat. Rev. Gastroenterol. Hepatol.* **2015**, *12*, 720–727.
- [3] Xavier, R. J.; Podolsky, D. K. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* **2007**, *448*, 427–434.
- [4] Chang John, T. Pathophysiology of Inflammatory Bowel Diseases. *New Engl. J. Med.* **2020**, *383*, 2652–2664.
- [5] Ni, J.; Wu, G. D.; Albenberg, L.; Tomov, V. T. Gut microbiota and IBD: causation or correlation? *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 573–584.
- [6] Mittal, M.; Siddiqui, M. R.; Tran, K.; Reddy, S. P.; Malik, A. B. Reactive Oxygen Species in Inflammation and Tissue Injury. *Antioxid. Redox Signaling* **2014**, *20*, 1126–1167.
- [7] Zhao, J.; Cai, X.; Gao, W.; Zhang, L.; Zou, D.; Zheng, Y.; Li, Z.; Chen, H. Prussian Blue Nanozyme with Multienzyme Activity Reduces Colitis in Mice. *ACS Appl. Mater. Interfaces* **2018**, *10*, 26108–26117.
- [8] Ungaro, R.; Mehandru, S.; Allen, P. B.; Peyrin-Biroulet, L.; Colombel, J.-F. Ulcerative colitis. *The Lancet* **2017**, *389*, 1756–1770.
- [9] Lou, J.; Duan, H.; Qin, Q.; Teng, Z.; Gan, F.; Zhou, X.; Zhou, X. Advances in Oral Drug Delivery Systems: Challenges and Opportunities. In *PHARMACEUTICS*, 2023; pp 484.
- [10] Zhang, W.; Michalowski, C. B.; Belouqui, A. Oral Delivery of Biologics in Inflammatory Bowel Disease Treatment. *Front. Bioeng. Biotechnol.* **2021**, *Volume 9* - 2021.
- [11] Lautenschläger, C.; Schmidt, C.; Fischer, D.; Stallmach, A. Drug delivery strategies in the therapy of inflammatory bowel disease. *Adv. Drug Del. Rev.* **2014**, *71*, 58–76.
- [12] Hou, J.; Zhao, M.; Zou, A.; Zhu, X.; Fu, R.; Xianyu, Y. A Microalgae-Probiotic-Nanozyme Robot for Alleviating Intestinal Inflammation and Microbiota Dysbiosis. *Adv. Mater.* **2025**, *37*, e08754.
- [13] Zhang, F.; Li, Z.; Chen, C.; Luan, H.; Fang, R. H.; Zhang, L.; Wang, J. Biohybrid Microalgae Robots: Design, Fabrication, Materials, and Applications. *Adv. Mater.* **2024**, *36*, 2303714.
- [14] Jin, Z.; Zhang, Y.; Hu, H.; Li, Q.; Zhang, L.; Zhao, K.; Liu, W.; Li, L.; Gao, C. Closed-loop theranostic microgels for immune microenvironment modulation and microbiota remodeling in ulcerative colitis. *Biomaterials* **2025**, *314*, 122834.
- [15] Salaritabar, A.; Darvishi, B.; Hadjiakhoondi, F.; Manayi, A.; Sureda, A.; Nabavi, S. F.; Fitzpatrick, L. R.; Nabavi, S. M.; Bishayee, A. Therapeutic potential of flavonoids in inflammatory bowel disease: A comprehensive review. *WORLD J GASTROENTERO* **2017**, *23*, 5097–5114.
- [16] Gao, X.; Feng, X.; Hou, T.; Huang, W.; Ma, Z.; Zhang, D. The roles of flavonoids in the treatment of inflammatory bowel disease and extraintestinal manifestations: A review. *Food Biosci.* **2024**, *62*, 105431.
- [17] Hoensch, H. P.; Weigmann, B. Regulation of the intestinal immune system by flavonoids and its utility in chronic inflammatory bowel disease. *WORLD J GASTROENTERO* **2018**, *24*, 877–881.
- [18] Gao, F.; Zhu, F.; Shuai, B.; Wu, M.; Wei, C.; Yuan, Y.; Gui, Y.; Tian, Y.; Fan, H.; Wu, H. Quercetin ameliorates ulcerative colitis by restoring the balance of M2/M1 and repairing the intestinal barrier via downregulating cGAS–STING pathway. *Front. Pharmacol.* **2024**, *Volume 15* - 2024.
- [19] Xiong, M.; Kuang, W.; Liu, Z.; Tong, R.; Deng, X.; Wang, N.; Wan, X.; Feng, M.; Luo, Y.; Zhang, B.; Zhang, Z.; Zheng, F. Quercetin alleviates ulcerative colitis via regulating gut microbiota and tryptophan metabolism. *MSYSTEMS* **2025**, *10*, e00703–00725.
- [20] Jiang, Z.; Yan, M.; Qin, Y.; Liu, Z.; Duan, Y.; Wang, Y.; Zhang, R.; Lin, W.; Li, Y.; Xie, T.; Ke, J. Quercetin alleviates ulcerative colitis through inhibiting CXCL8-CXCR1/2 axis: a network and transcriptome analysis. **2024**,

- Volume 15 - 2024.*
- [21] Wang, W.;Sun, C.;Mao, L.;Ma, P.;Liu, F.;Yang, J.; Gao, Y. The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. *Trends Food Sci. Technol.* **2016**, *56*, 21-38.
- [22] Lin, Z.;Zhao, Z.;Lin, X.;Yang, Z.;Wang, L.;Xi, R.; Long, D. Advances in oral treatment of inflammatory bowel disease using protein-based nanoparticle drug delivery systems. *Drug Deliv.* **2025**, *32*, 2544689.
- [23] Li, Y.;Xu, Z.;Zhao, S.;Huang, T.;Xu, J.;Wang, S.;Sang, Y.;Yu, W.; Wang, X. Oral administration of curcumin and quercetin nanoparticles can improve ulcerative colitis by regulating intestinal microorganisms. *Front. Nutr.* **2025**, *Volume 12 - 2025*.
- [24] Min, D. K.;Kim, Y. E.;Kim, M. K.;Choi, S. W.;Park, N.; Kim, J. Orally Administreated Inflamed Colon-Targeted Nanotherapeutics for Inflammatory Bowel Disease Treatment by Oxidative Stress Level Modulation in Colitis. *ACS Nano* **2023**, *17*, 24404-24416.
- [25] Bai, Y.;Jiang, D.;Wu, B.;Peng, J.;Wang, J.;Chen, Y.; Li, X. Enhanced precise therapy of ROS-sensitive dual-layer shell nanoparticles loading quercetin on DSS-induced ulcerative colitis mice. *APL Mater.* **2025**, *13*, 011121.
- [26] Cao, Z.;Wang, X.;Pang, Y.;Cheng, S.; Liu, J. Biointerfacial self-assembly generates lipid membrane coated bacteria for enhanced oral delivery and treatment. *Nat. Commun.* **2019**, *10*, 5783.
- [27] Zhu, Y.-X.;You, Y.;Chen, Z.;Xu, D.;Yue, W.;Ma, X.;Jiang, J.;Wu, W.;Lin, H.; Shi, J. Inorganic Nanosheet-Shielded Probiotics: A Self-Adaptable Oral Delivery System for Intestinal Disease Treatment. *Nano Lett.* **2023**, *23*, 4683-4692.
- [28] Zhao, H.;Du, Y.;Liu, L.;Du, Y.;Cui, K.;Yu, P.;Li, L.;Zhu, Y.;Jiang, W.;Li, Z.;Tang, H.; Ma, W. Oral nanozyme-engineered probiotics for the treatment of ulcerative colitis. *J. Mater. Chem. B* **2022**, *10*, 4002-4011.
- [29] Cao, F.;Jin, L.;Gao, Y.;Ding, Y.;Wen, H.;Qian, Z.;Zhang, C.;Hong, L.;Yang, H.;Zhang, J.;Tong, Z.;Wang, W.;Chen, X.; Mao, Z. Artificial-enzymes-armed Bifidobacterium longum probiotics for alleviating intestinal inflammation and microbiota dysbiosis. *Nature Nanotechnology* **2023**, *18*, 617-627.
- [30] Pan, J.;Qian, H.;Sun, Y.;Miao, Y.;Zhang, J.; Li, Y. Microbially synthesized nanomaterials: Advances and applications in biomedicine. *Precision Medicine and Engineering* **2025**, *2*, 100019.
- [31] Li, J.;Dekanovsky, L.;Khezri, B.;Wu, B.;Zhou, H.; Sofer, Z. Biohybrid Micro- and Nanorobots for Intelligent Drug Delivery. *Cyborg Bionic Syst* **2022**, *2022*.
- [32] Zhang, F.;Zhuang, J.;Li, Z.;Gong, H.;de Ávila, B. E.-F.;Duan, Y.;Zhang, Q.;Zhou, J.;Yin, L.;Karshalev, E.;Gao, W.;Nizet, V.;Fang, R. H.;Zhang, L.; Wang, J. Nanoparticle-modified microrobots for in vivo antibiotic delivery to treat acute bacterial pneumonia. *Nat. Mater.* **2022**, *21*, 1324-1332.
- [33] Kang, J.;Yang, Z.;Li, L.;Wang, Y.;Wu, Z.;Ding, G.;Cen, R.; Zhang, C. Application of microalgae as functional biomaterials for tissue repair and regeneration. *Acta Biomater.* **2026**, *209*, 102-119.
- [34] Sycuro, L. K.;Pincus, Z.;Gutierrez, K. D.;Biboy, J.;Stern, C. A.;Vollmer, W.; Salama, N. R. Peptidoglycan crosslinking relaxation promotes *Helicobacter pylori*'s helical shape and stomach colonization. *Cell* **2010**, *141*, 822-833.
- [35] Celli, J. P.;Turner, B. S.;Afdhal, N. H.;Keates, S.;Ghiran, I.;Kelly, C. P.;Ewoldt, R. H.;McKinley, G. H.;So, P.;Erramilli, S.; Bansil, R. *Helicobacter pylori* moves through mucus by reducing mucin viscoelasticity. *PNAS* **2009**, *106*, 14321-14326.
- [36] Decuzzi, P.; Ferrari, M. The adhesive strength of non-spherical particles mediated by specific interactions. *Biomaterials* **2006**, *27*, 5307-5314.
- [37] Champion, J. A.;Katare, Y. K.; Mitragotri, S. Particle shape: A new design parameter for micro- and nanoscale drug delivery carriers. *J. Controlled Release* **2007**, *121*, 3-9.
- [38] Huang, H.;Lang, Y.; Zhou, M. A comprehensive review on medical applications of microalgae. *Algal Res.* **2024**, *80*, 103504.
- [39] Huang, H.;Lang, Y.;Wang, S.; Zhou, M. Microalgae-based drug delivery systems in biomedical applications. *Eng Regen* **2024**, *5*, 361-374.
- [40] Ye, J.;Sun, H.;Zhang, Q.;He, J.; Zhou, M. Microalgae-based Intestinal villi-targeting multistage biosystem for irritable bowel syndrome treatment. *Nat. Commun.* **2025**, *16*, 7614.
- [41] Ma, L.;Su, C.-R.;Li, S.-Y.;He, S.;Nag, A.; Yuan, Y. Co-delivery of curcumin and quercetin in the bilayer structure based on complex coacervation. *Food Hydrocoll.* **2023**, *144*, 108907.
- [42] Kamguyan, K.;Torp, A. M.;Christfort, J. F.;Guerra, P. R.;Licht, T. R.;Hagner Nielsen, L.;Zor, K.; Boisen, A. Colon-Specific Delivery of Bioactive Agents Using Genipin-Cross-Linked Chitosan Coated Microcontainers. *ACS Applied Bio Materials* **2021**, *4*, 752-762.
- [43] Xiao, M.;Wu, S.;Cheng, Y.;Ma, J.;Luo, X.;Chang, L.;Zhang, C.;Chen, J.;Zou, L.;You, Y.; Zhang, J. Colon-specific delivery of isoliquiritigenin by oral edible zein/caseate nanocomplex for ulcerative colitis treatment. **2022**, *Volume 10 - 2022*.
- [44] dos Santos, A. M.;Carvalho, S. G.;Meneguim, A. B.;Sábio, R. M.;Gremião, M. P. D.; Chorilli, M. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal diseases therapy: Challenges, advances and future perspectives. *J. Controlled Release* **2021**, *334*, 353-366.
- [45] Kumar, A.;Singh, N. K.;Wadhwa, S.;Kumar, R.;Mohd, S.; Harish, V. Advancing colon targeting: Natural polymer systems for drug delivery. *Eur. Polym. J.* **2026**, *242*, 114459.
- [46] Wells, M. L.;Potin, P.;Craigie, J. S.;Raven, J. A.;Merchant, S. S.;Helliwell, K. E.;Smith, A. G.;Camire, M. E.; Brawley, S. H. Algae as nutritional and functional food sources: revisiting our understanding. *J. Appl. Phycol.* **2017**, *29*, 949-982.
- [47] Song, Y.;Hu, Z.;Liu, S.;Luo, S.;He, R.;Yang, X.;Li, S.;Yang, X.;An, Y.; Lu, Y. Utilization of Microalgae and Duckweed as Sustainable Protein Sources for Food and Feed: Nutritional Potential and Functional Applications. *J. Agric. Food Chem.* **2025**, *73*, 4466-4482.
- [48] Zhang, D.;Zhong, D.;Ouyang, J.;He, J.;Qi, Y.;Chen, W.;Zhang, X.;Tao, W.; Zhou, M. Microalgae-based oral microcarriers for gut microbiota homeostasis and intestinal protection in cancer radiotherapy. *Nat. Commun.* **2022**, *13*, 1413.
- [49] Zhong, D.;Zhang, D.;Chen, W.;He, J.;Ren, C.;Zhang, X.;Kong, N.;Tao, W.; Zhou, M. Orally deliverable strategy based on microalgal biomass for intestinal disease treatment. *Sci. Adv.* **2021**, *7*, eabi9265.

Electronic Supplementary Material

Bio-inspired helical microcarriers anchoring quercetin nanoparticles enable prolonged and self-trackable colonic delivery in colitis

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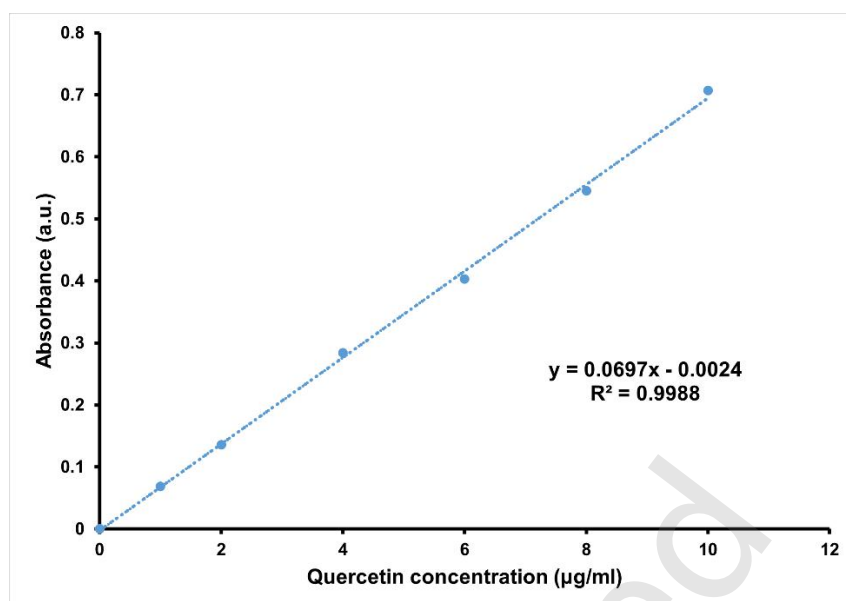


Figure S1: Standard calibration curve of quercetin. Absorbance was measured at 374 nm in ethanol via UV-vis spectrophotometry.

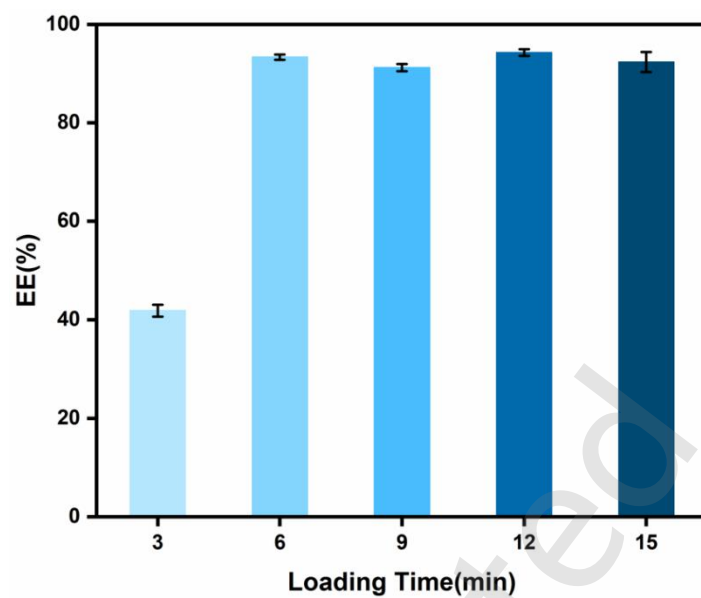


Figure S2: Binding efficiency of QUEnano onto SP at various incubation times. Data are presented as mean $\pm$ SD (n = 3).

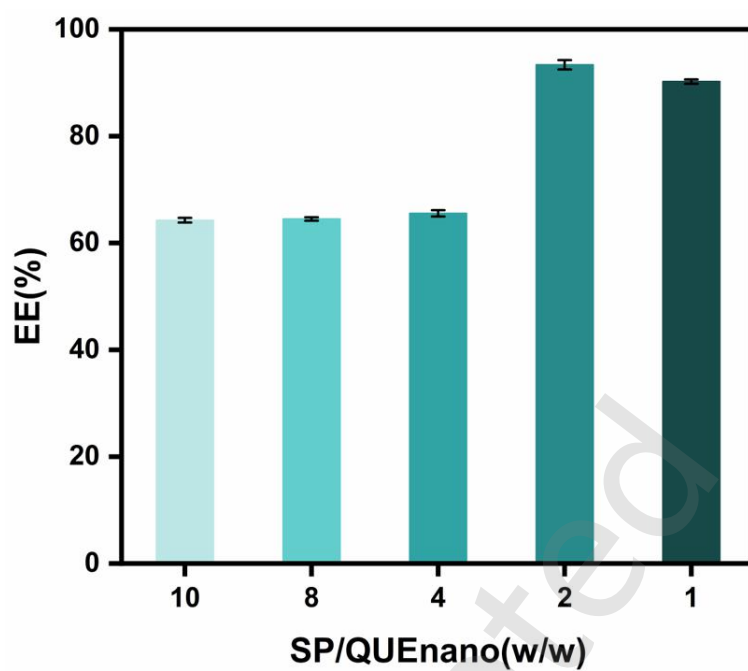


Figure S3: Drug loading efficiency of the QUE@SP composites prepared at various mass ratios of SP to QUE nano. Data are presented as mean $\pm$ SD (n = 3).

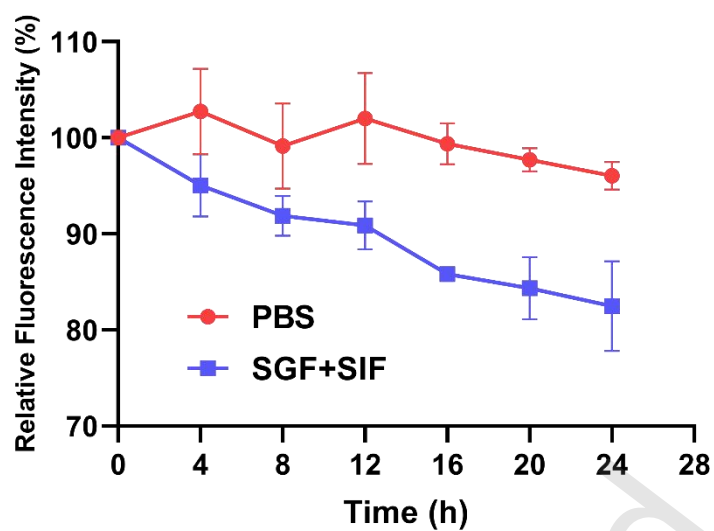


Figure S4: Relative fluorescence intensity of QUE@SP during incubation in PBS and sequential simulated gastrointestinal fluids (SGF+SIF) over 24 h (n=3).

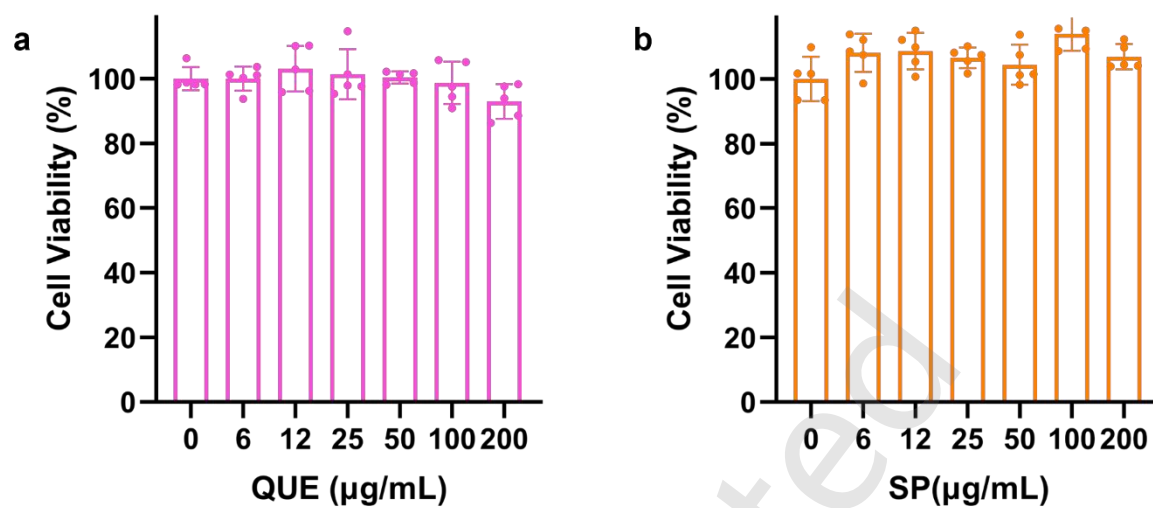


Figure S5: Cell viability of IEC-6 cells incubated with (a) QUE and (b) SP at various concentrations (0, 6, 12, 25, 50, 100, and 200 $\mu\text{g/mL}$). Data are presented as mean $\pm$ SD (n = 5).

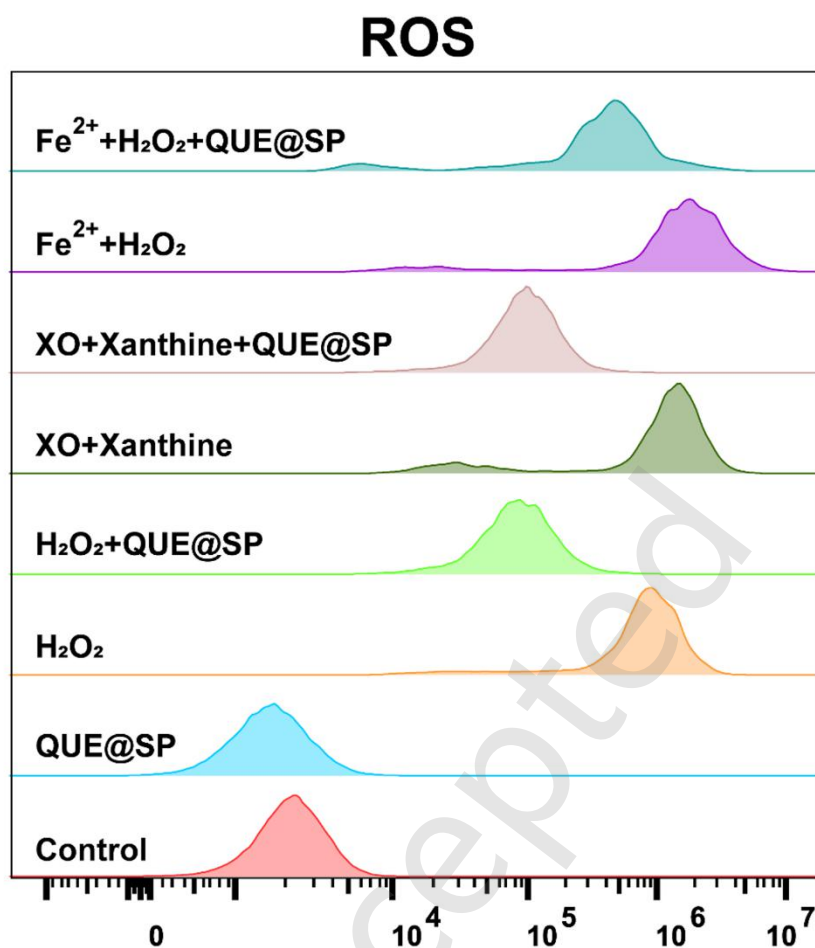


Figure S6: Flow cytometry analysis of intracellular ROS levels in IEC-6 cells stained with the DCFH-DA probe under various oxidative stress conditions (H_2O_2 , XO + Xanthine, and $\text{Fe}^{2+} + \text{H}_2\text{O}_2$) with or without QUE@SP treatment.

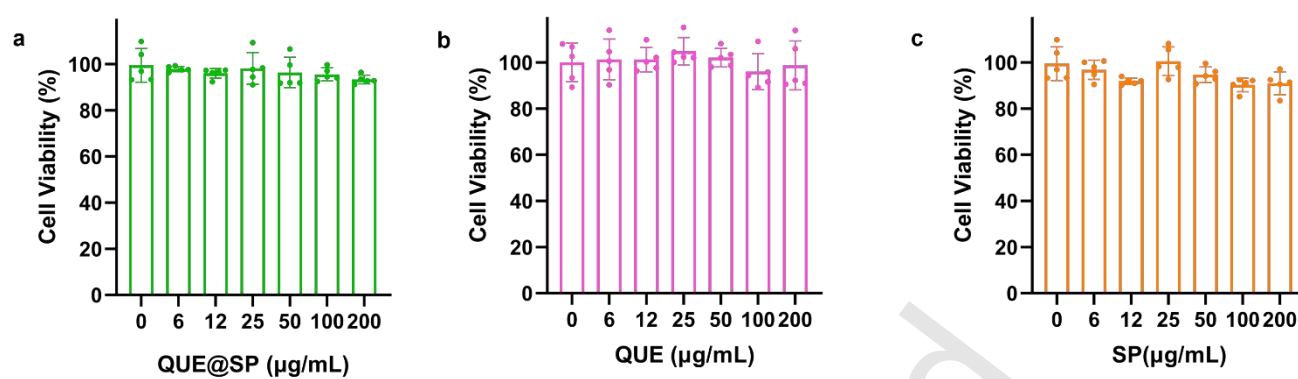


Figure S7: Cell viability of RAW 264.7 cells incubated with (a) QUE@SP, (b) QUE, and (c) SP at various concentrations (0, 6, 12, 25, 50, 100, and 200 $\mu\text{g/mL}$). Data are presented as mean $\pm$ SD (n = 5).

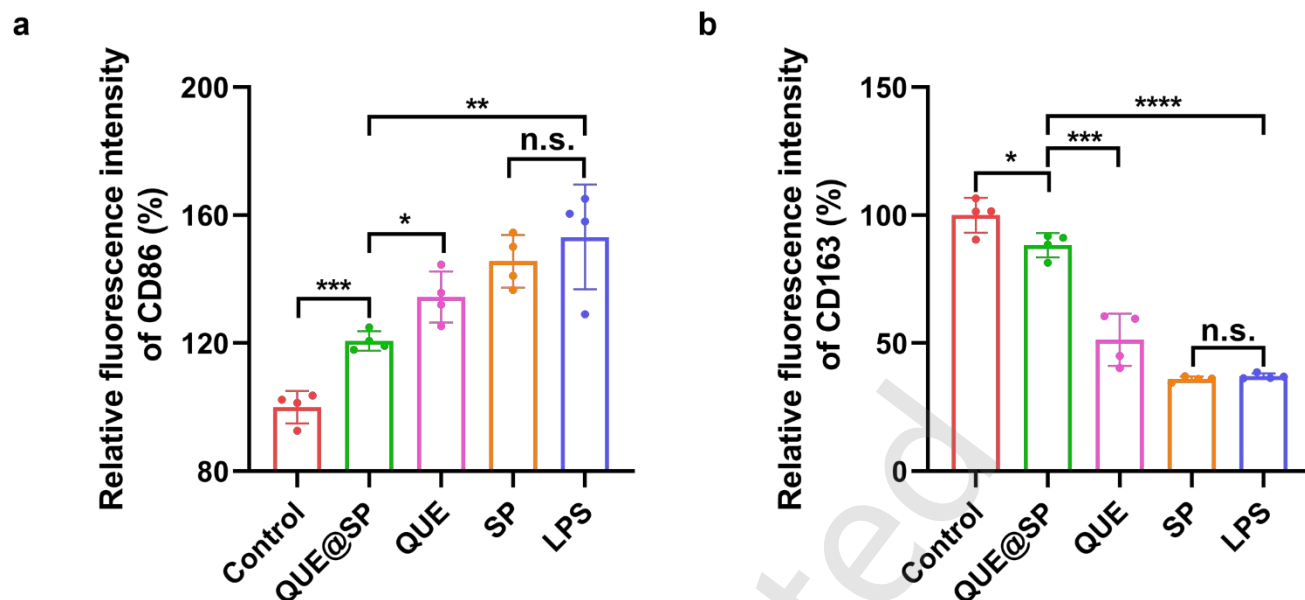


Figure S8: Quantitative analysis of the M1 macrophage marker CD86 (a) and the M2 macrophage marker CD163 (b) after treatment with QUE, SP, and QUE@SP. Data are presented as mean $\pm$ SD (n = 4; *P < 0.05, P < 0.01, ***P < 0.001, ****P < 0.0001; n.s., not significant).

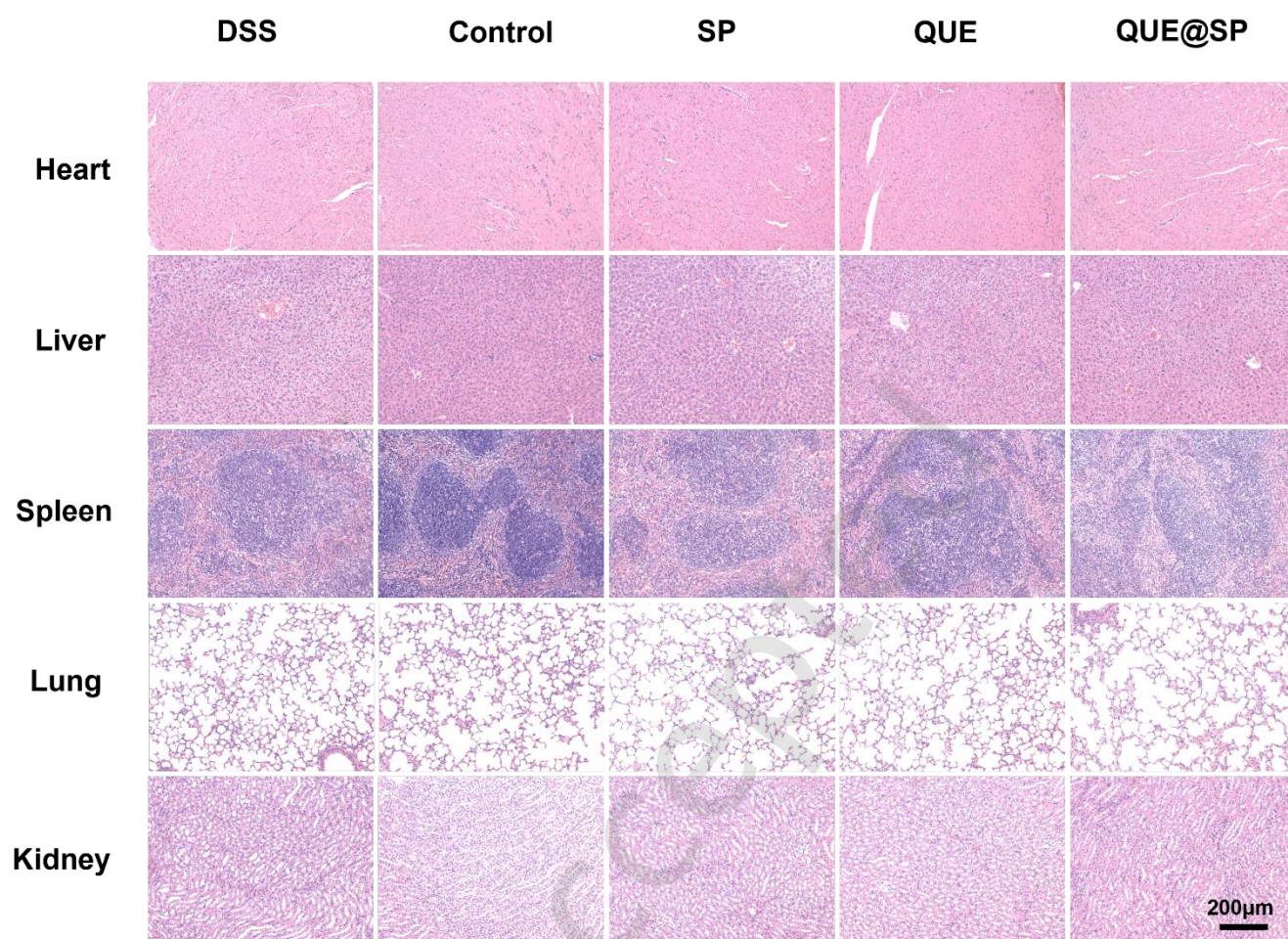


Figure S9: H&E tissue staining sections of heart, liver, spleen, lung, and kidney from mice in different treatment groups. (scale bar: 200 μ m)

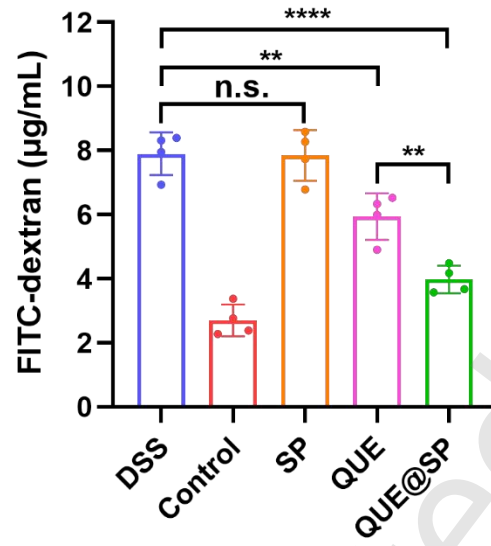


Figure S10: Concentration of FITC-dextran in the serum of mice. Data are presented as mean $\pm$ SD ($n = 4$; $P < 0.01$, $***P < 0.001$, $****P < 0.0001$; n.s., not significant).

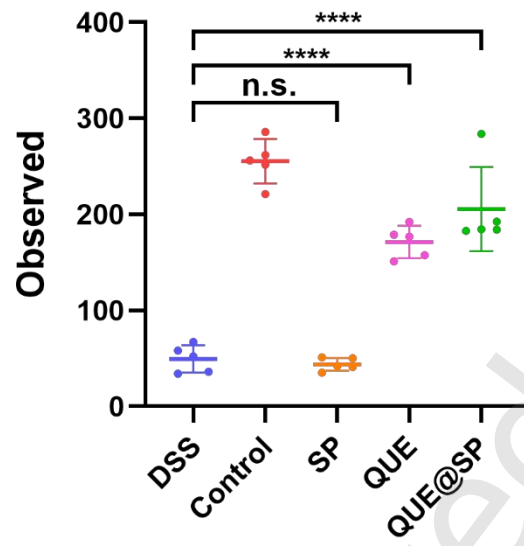


Figure S11: Observed OTUs index of the gut microbiota. Data are presented as mean $\pm$ SD (n = 5; *P < 0.05, P < 0.01, ***P < 0.001, ****P < 0.0001; n.s., not significant).

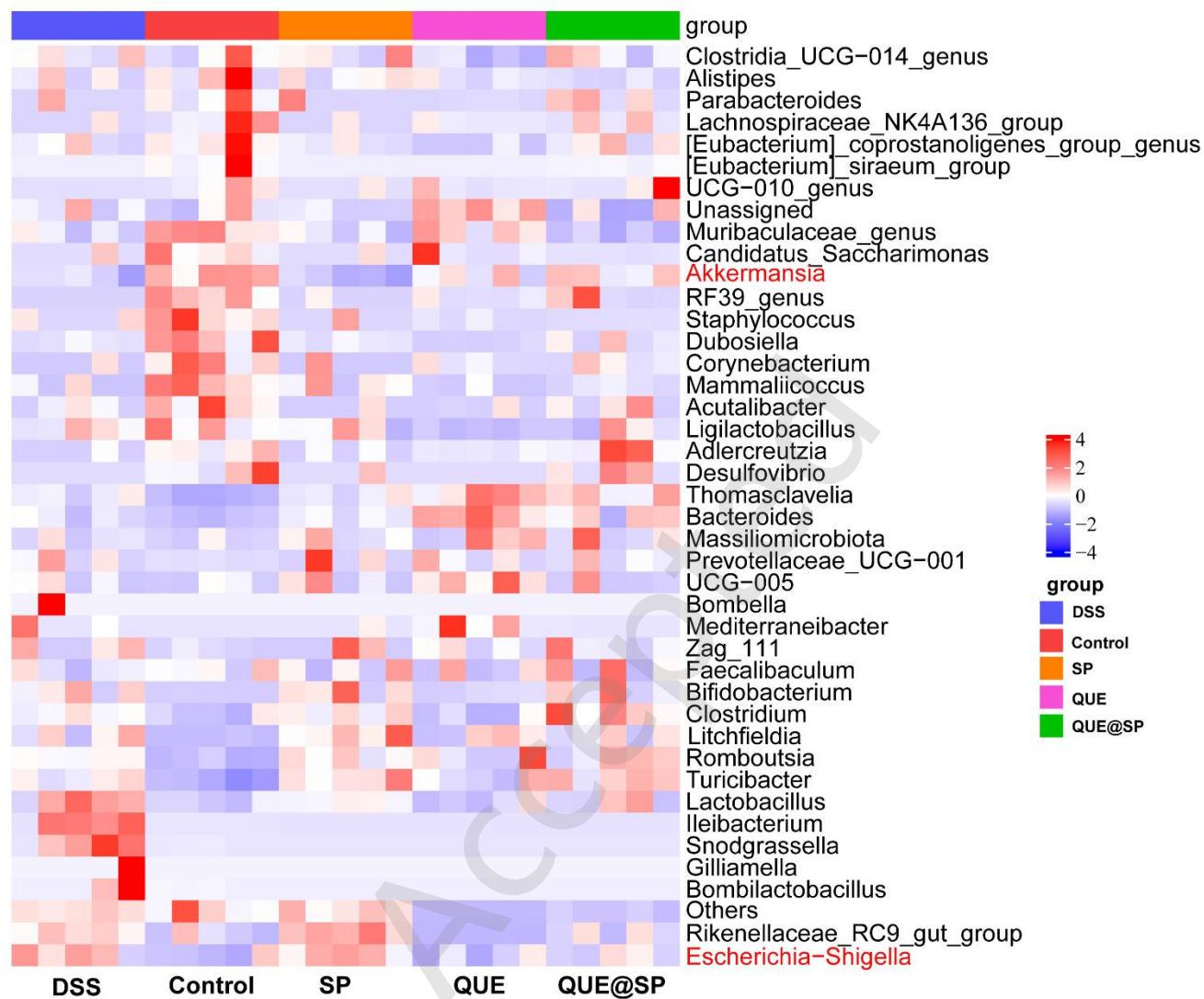


Figure S12: Taxonomic profiling of the gut microbiota at the genus level.

Table S1. The scoring system of DAI

Score	Body weight loss	Stool consistency	Blood
0	≤1%	Normal	Negative hemocult
1	1-5%	Soft but formed	
2	5-10%	Soft	Positive hemocult
3	10-15%	Very soft	
4	>15%	Watery diarrhea	Blood traces in stool visible

DAI score = (Body weight loss score + Stool consistency score + Blood score)/3

Table S2. Histological scoring system of colon

Score	Inflammation	Depth of lesion	Crypt damage	Area of lesion
0	Normal	Normal	Normal	≤1%
1	Mild	Submucosa	1/3 crypts	1-25%
2	Moderate	Muscularis	2/3 crypts	25-50%
3	Severe	Serosa	All, intact epithelium	50-75%
4	Extremely severe		All, destroyed epithelium	>75%

Histological score = (Inflammation score + Depth of lesion score + Crypt damage score) × Area of lesion score