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ORIGINAL ARTICLE

Protective effects of sinomenine against dextran sulfate sodium-induced ulcerative colitis in rats via alteration of HO-1/Nrf2 and inflammatory pathway

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Abstract

Background Dextran Sulfate Sodium (DSS) induces ulcerative colitis (UC), a type of inflammatory bowel disease (IBD) that leads to inflammation, swelling, and ulcers in the large intestine. The aim of this experimental study is to examine how sinomenine, a plant-derived alkaloid, can prevent or reduce the damage caused by DSS in the colon and rectum of rats.

Material and methods Induction of ulcerative colitis (UC) in rats was achieved by orally administering a 2% Dextran Sulfate Sodium (DSS) solution, while the rats concurrently received oral administrations of sinomenine and sulfasalazine. The food, water intake was estimated. The body weight, disease activity index (DAI), colon length and spleen index estimated. Antioxidant, cytokines, inflammatory parameters and mRNA expression were estimated. The composition of gut microbiota was analyzed at both the phylum and genus levels in the fecal samples obtained from all groups of rats.

Results Sinomenine treatment enhanced the body weight, colon length and reduced the DAI, spleen index. Sinomenine treatment remarkably suppressed the level of NO, MPO, ICAM-1, and VCAM-1 along with alteration of antioxidant parameters such as SOD, CAT, GPx, GR and MDA. Sinomenine treatment also decreased the cytokines like TNF-α, IL-1, IL-1β, IL-6, IL-10, IL-17, IL-18 in the serum and colon tissue; inflammatory parameters viz., PAF, COX-2, PGE_2, iNOS, NF-κB; matrix metalloproteinases level such as MMP-1 and MMP-2. Sinomenine significantly ($P < 0.001$) enhanced the level of HO-1 and Nrf_2. Sinomenine altered the mRNA expression of RIP1, RIP3, DRP3, NLRP3, IL-1β, caspase-1 and IL-18. Sinomenine remarkably altered the relative abundance of gut microbiota like firmicutes, Bacteroidetes, F/B ratio, Verrucomicrobia, and Actinobacteria.

Conclusion The results clearly indicate that sinomenine demonstrated a protective effect against DSS-induced inflammation, potentially through the modulation of inflammatory pathways and gut microbiota.

Keywords Ulcerative colitis · Sinomenine · Inflammation · Cytokines · Antioxidant · Gut microbiota

Introduction

The gastrointestinal tract (GIT) is mainly affected by ulcerative colitis (UC), a common inflammatory condition (Mahmoud et al. 2021). It is characterized by a chronic and relapsing pattern, often causing nonspecific yet severe effects on the affected individuals. This condition leads to inflammation and ulceration of the colon's innermost lining, causing a range of gastrointestinal symptoms and potentially impacting a patient's overall health and quality of life (Morsy et al. 2019; Gao et al. 2022). Effective management and treatment of UC are essential to provide relief and minimize the impact of its symptoms on those affected. Patients suffer from the UC exhibit the various clinical symptoms like weight loss, fecal blood, abdominal pain and diarrhea.

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The precise mechanisms underlying the pathogenesis of UC remain to be fully elucidated, there is substantial evidence pointing toward the dysregulation of the host immune system as a central component in the development of UC (Mahmoud et al. 2021).

Nevertheless, it is important to note that persistent intestinal inflammation stands out as one of the primary clinical features deeply involved in both the pathogenesis and potential complications of UC (Xu et al. 2012; Kim 2015). During intestinal inflammation, there is an increase in the production of inflammatory cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), 6, and 18. These factors collectively contribute to the amplification of the inflammatory response, leading to increased severity of colitis. Furthermore, the activation of the NOD-like receptor pyrin domain-containing protein (NLRP3) inflammasome pathway plays a crucial role in the pathogenesis of intestinal inflammation in both preclinical and clinical models (Kim 2015; Mahmoud et al. 2021). It is well known that inflammasome serves as a crucial component of the innate immune defense system. Under conditions of stress or cellular infection, protein complexes that include NOD-like receptors (NLRs) become activated, leading to the formation of inflammasomes. During the UC, the activated NLRP3 inflammasome boosts the maturation of IL1β and IL-18, which is remarkably increased during the progression of IBD. Furthermore, results from genome-wide association studies (GWAS) have revealed a significant

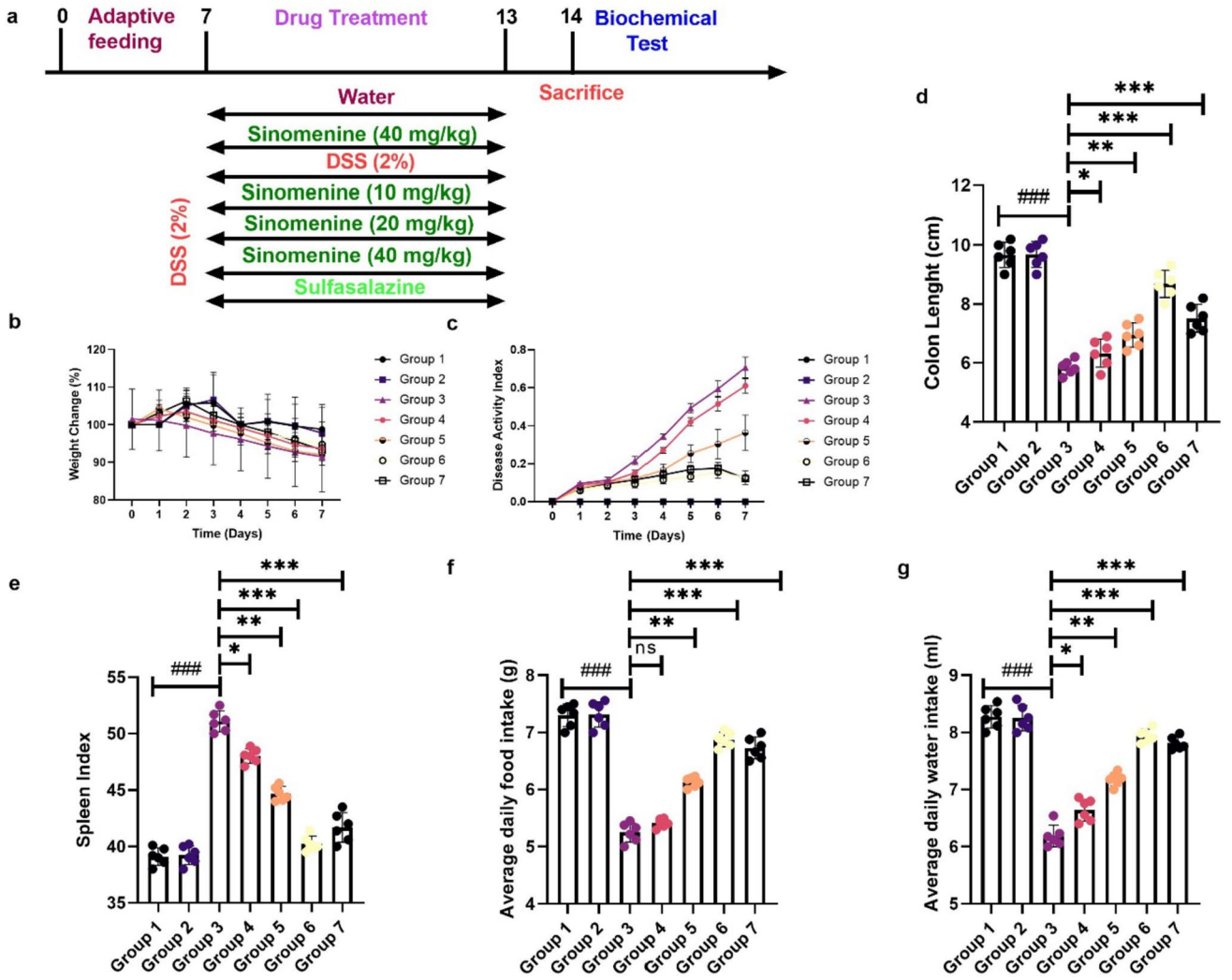

Fig. 1 Effect of sinomenine intake on body weight, disease activity index, colon length, and spleen index against DSS-induced UC in rats. **a** schematic diagram of this experiment, **b** weight change, **c** disease activity index, **d** colon length, **e** spleen index, **f** average daily food intake, and **g** average daily water intake. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

association between the NLRP3 gene and IBD. As a result, it becomes imperative to target the pathogenic role of the NLRP3 inflammasome to curtail intestinal inflammation and mitigate the risk of colon cancer development in the progression of IBD (Yu et al. 2023). NLRP3 inflammasome agonists are various like bacterial toxins, microcrystalline substances, and adenosine triphosphate (ATP). Previous reports suggest that various NLRP3 agonists can induce the mitochondrial injury, resultant in the secretion of fragmented mitochondrial DNA (mtDNA) and mitochondrial reactive oxygen species (mtROS) (Bai et al. 2021; Yu et al. 2023). Moreover, increasing the mitochondrial injury prevents activation of NLRP3 inflammasome. As part of the process involved in maintaining mitochondrial homeostasis, mitophagy is activated to eliminate damaged mitochondria. The damaged mitochondria undergo ubiquitination facilitated by the E3 ubiquitin ligase Parkin. This ubiquitination event leads to the translocation of ubiquitin-binding autophagy receptors to the mitochondria (Kim et al. 2016; Biasizzo and Kopitar-Jerala 2020). Subsequently, these ubiquitinated mitochondria are engulfed by autophagosomes, thus initiating the process of mitophagy. As a result, the initiation of mitophagy represents a crucial pathway for inhibiting the activation of the NLRP3 inflammasome (Kim et al. 2016; Biasizzo and Kopitar-Jerala 2020; Yu et al. 2023).

Inflammatory reactions are controlled by the nuclear transcription factor-kappa B (NF-κB) pathway, which is essential for this function. In the context of UC, NF-κB becomes activated and translocates to the nucleus, where it binds to DNA binding sites, thereby triggering the production of essential immune mediators (Cao et al. 2018; Liu et al. 2018). According to recent studies, NF-κB is involved in the development of UC, and blocking NF-κB can improve the condition of colitis. Moreover, Nrf2, a key transcription factor that protects against oxidative stress and inflammation, also has a role in the onset of UC (Liu et al. 2018; Peng et al. 2023). Notably, Nrf2 and NF-κB are regarded as promising targets for molecular therapy in the context of UC (Liu et al. 2018).

Rodents with colitis induced by DSS are often used as a model, as they have a similar condition to human UC (Okayasu et al. 1990). This model aligns closely with the clinical manifestations of human UC, making it a promising and dependable model for conducting research on this disease. During the DSS-induced UC model, leukocytes such as lymphocytes, macrophages, and neutrophils have been found in the infiltrate inflamed tissue (Zhao et al. 2013; Qu et al. 2020). Concurrently, there are various ROS found in the colonic mucosa. Oxidative stress, with its dual effect via increased the production of free radical and lipid peroxidation. The production and secretion of ROS via immune cells appear to play a significant role in the pathophysiology of UC (Zhao et al. 2013; Qu et al. 2020; Yu et al. 2023).

A plant called Sinomenium acutum is the source of sinomenine, a compound that has the chemical formula 7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methyl-9a, 13a, 14a-morphinan-6-one (Zhou et al. 2020; Li et al. 2021). Sinomenine is a widely recognized herb in traditional Chinese medicine, frequently employed by Chinese practitioners to address various ailments, including arthritis (Lu et al. 2022). In addition, sinomenine has demonstrated anti-inflammatory and analgesic effects. Sinomenine has been widely used for several decades to treat various kidney diseases, such as autoimmune nephritis, allograft rejection, mesangial proliferative nephritis, and chronic glomerulonephritis. It also has anti-inflammatory effects, such as decreasing the growth of lymphocytes and synovial fibroblasts, preventing macrophages from entering the tissues, and lowering the levels of inflammatory cytokines (Zhang et al. 2012; Yuan et al. 2018; Li et al. 2021, 2023; Lu et al. 2022). The protective role of sinomenine in DSS-induced UC has not been well-studied. This study explores how sinomenine can protect against DSS-induced UC in rats and reveals the mechanisms behind it.

Material and methods

Experimental rodents

The departmental animal house supplied male Swiss albino rats, 12–14 weeks old and 200 ± 20 g in weight, for this study. The rats lived in polyethylene cages by themselves under standard laboratory conditions, with a temperature of 22 ± 5 °C, relative humidity of 50–70%, and a light–dark cycle of 12/12 h. The rats had access to purified water and pelleted food for the whole study. The Institutional Animal Ethical Committee's guidelines and the Committee for the

Table 1 Index of disease activity index score (DAI)

S. No	Score	Weight loss	Stool constituency	Bleeding
1	0	Normal	Normal (well-formed pellets)	Not observed
2	1	1–5%	Normal	Not observed
3	2	6–10%	Loose (pasty stools that do not stick to the anus)	Occult
4	3	11–15%	Loose (pasty stools that do not stick to the anus)	Occult
5	4	> 15%	Diarrhea (liquid stools that stick to the anus)	Gross bleeding

Purpose of Control and Supervision of Experiments on Animals' recommendations were followed by the entire experimental protocol. This study has been approved by the Ethics Committee of Jinan Central Hospital (AF/SC-04/09.0).

Toxicant preparation

All rat groups, except the normal control group, received the oral administration of 2% DSS solution in drinking water from day 7 to day 13 to induction the acute colitis (Fig. 1a). The rats were put to death on day 14, and parts of their colon were taken for analysis of macroscopic and other parameters (Patel et al. 2022).

Experimental design

The rats were split into five groups of six rats each as follows:

- Group 1: normal control (received tap water),
- Group 2: DSS control (2%)
- Group 3: DSS + Sinomenine (10 mg/kg),
- Group 4: DSS + Sinomenine (20 mg/kg),
- Group 5: DSS + Sinomenine (40 mg/kg), and
- Group 6: DSS + sulfasalazine (standard drug), respectively.

Evaluation parameters

Food and water intake

During the experimental study, the water and food intake were estimated daily basis in all groups of rats (Patel et al. 2022).

Body weight

The body weight of all groups of rats was measured daily. The percentage changes in body weight were calculated by assessing the difference between the initial and final body weights of the animals (Patel et al. 2022).

Disease activity index

Previous reported method was used for the scrutinized the disease activity index (DAI) and extent of intestinal inflammation based on the grading system (Kihara et al. 2003; Cao et al. 2018) (Table 1).

Colon length

The rats were put to death on the last day of the experiment (day 11), and the colon tissue was quickly cut out. The length of the colon was measured by placing it on graph paper and using a standard ruler for reference. The weight of the colon was determined using a sensitive weighing balance (Patel et al. 2022).

Colon mucosal injury index

A 10 cm piece of the colon was cut out, washed with salt water, and split in the middle to measure the colon mucosal injury index. The colon segment's inner side was scored by looking at it.

Serum preparation

For the estimation of serum parameters, the rats were anesthetized using the diethyl ether for anesthesize the rats and

Table 2 List of primers

S. No	Gene	Primers (5′–3′)	
		Forward	Reverse
1	Drp1	ACACGATTGAAGGAACCGCA	CGCTTAATCTGACGTTTGACC
2	RIP1	CCTTCTTGCCCAGGAGAATGA	CTCTGAGGCGATCTGACGAC
3	RIP3	CGTAGACGTCGGGTTTCCAG	ACCAGTAGGCCATAACTTGACA
4	NLRP3	TCTGCACCCGGACTGTAAAC	CACCCAACTGTAGGCTCTGC
5	COX-2	TGTATGCTACCATCTGGCTTCGG	GTTTGGAACAGTCGCTCGTCATC
6	NF-κB	CTGCGATACCTTAATGACAGCG	AATTTTGGCTTCCTTTCTTGGCT
7	Nrf2	TTGTAGATGACCATGAGTCGC	TGTCCTGCTGTATGCTGCTT
8	TNFα	GGCATGGATCTCAAAGACAACC	CAAATCGGCTGACGGTGTG
9	IL-1β	ATAGGCTCATCTGGGATCCTCT	ACAGGTCATTCTCATCACTGTCAA
10	IL-6	TGATGGATGCTTCCAAACTG	GAGCATTGGAAGTTGGGGTA
11	IL-18	ACAGGCCTGACATCTTCTGC	ATTGTTCCTGGGCCAAGAGG
12	Caspase-1	TGCCCAGAGCACAAGACTTC	TCCTTGTTTCTCTCCACGGC
13	β-Actin	GACGGCCAGGTCATCACTATTG	CCACAGGATTCCATACCCAAGA

blood samples were collected via puncturing the retroorbital plexus. The blood samples were collected in the test tube and centrifuged at 10,000 rpm for 15 min at 12,000*g* rpm at 37 °C to separate the serum. The serum was collected and stored at − 20 °C for further biochemical analysis. For the collection of colon tissue, the rats were decapitated using the 10 mg/kg xylazine and 60 mg/kg ketamine and colon tissue 10 cm was taken from the distal colon via washing with the physiological saline solution.

MPO activity

The O-dianisidine method was employed to assess MPO activity, utilizing the MPO detection kit. Colon tissue samples were weighed and homogenized in a solution of ice-cold physiological saline at a ratio of 9 volumes to the weight of the tissue (w/v). Spectrophotometry was used to measure the absorbance at 460 nm. The amount of peroxide that 1 µmol of enzyme can break down per minute at 37 °C was used to calculate MPO activity. The results were shown as units per gram of tissue (U/g tissue).

NO estimation

The level of NO was estimated via estimation of its stable metabolites, nitrate (NO_3^-) and nitrite (NO_2^-), based on the using the previous reported method with minor modification (Miranda et al. 2001; Zhao et al. 2013). Briefly, 20% of colonic homogenate (0.1 ml) was mixed to the methylalcohol (0.1 ml) and centrifuged for 10 min at 12,000*g* rpm for 15 min. A volume of 0.01 ml of the resulting supernatant was extracted and mixed with vanadium (III) chloride (0.1 ml). Afterthat, 50 µl of *N*-(1-naphthyl)ethylenediamine dihydrochloride (NEDD) and 50 µl of sulphanilamide solution were added and incubated for 30 min at 37 °C. The optical density was estimated at 540 nm against a blank using the UV spectrophotometer.

Antioxidant parameters

The kits were used to measure the antioxidant parameters such as GPx (MAK437), CAT (EZHL-80SK), GR (GRSA), SOD (19160) and MDA (MAK085) according to the manufacture instruction (Sigma Aldrich, USA).

TXB2 and LTC4

The level of TXB2 (MBS9327599) and LTC4 (MBS730206) were estimated using the manufacture instruction (MyBioSource, Inc., San Diego, USA).

ICAM-1 and VCAM-1

The level of ICAM-1 (MBS160081) and VCAM-1 (MBS175995) were estimated using the manufacture instruction (MyBioSource, Inc., San Diego, USA).

Cytokines

ELISA was used to measure the level of cytokines like interleukin (IL)-1, 1β, 2, 6, 10, 17 and tumor necrosis factor-α (TNF-α) according to the manufacture instruction (MyBioSource, Inc., San Diego, USA).

Inflammatory parameters

ELISA was used to measure the level of inflammatory parameters such as cyclooxygenase-2 (COX-2), inducible nitric oxide (iNOS), prostaglandin (PGE2), and nuclear factor-kappa B (NF-κB) according to the manufacture instruction (MyBioSource, Inc., San Diego, USA).

HO-1 and Nrf2

The level of HO-1 and Nrf2 were estimated using the manufacture instruction (MyBioSource, Inc., San Diego, USA).

mRNA expression

The total mRNA was isolated from colon tissue using a commercial kit according to the manufacturer's instructions (QIAGEN RNeasy). The cDNA was synthesized and amplified using the QIAGEN Quantitect® 205,313 kit and

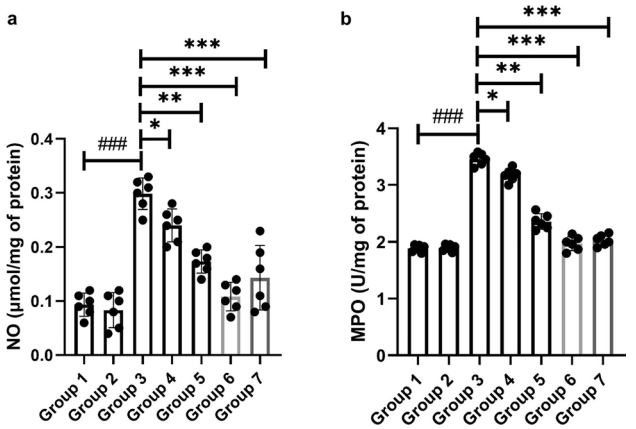

Fig. 2 Effect of sinomenine intake on NO and MPO level against DSS-induced UC in rats. **a** NO and **b** MPO. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

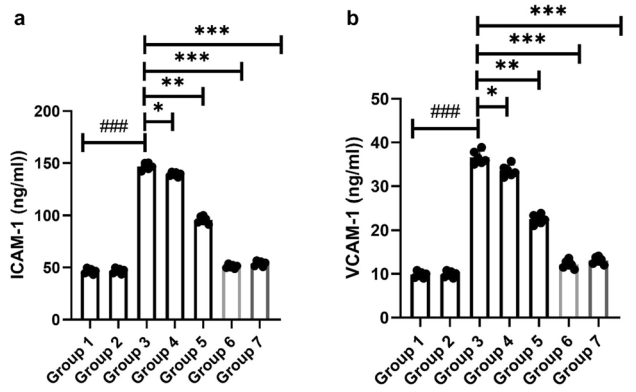

Fig. 3 Effect of sinomenine intake on ICAM-1 and VCAM-1 level against DSS-induced UC in rats. **a** NO and **b** MPO. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

Power SYBR Green PCR master mix with specific primers (Eurofins Genomics) in an RT-PCR LightCycler® 96 System (Roche, USA). The mRNA expression levels listed in Table 2 were determined using the ΔΔCt method and normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as a housekeeping gene.

Gut microbiota

Stool sample of the all-group rats were collected and QAIGEN kit was used to isolate the DNA via following the manufacture instruction. Brifely, the 250–300 mg stool sample were extracted from the lower intestine and placed in the 2 ml tube and thawed on ice. Afterward, ASL buffer (1.5 ml) was added and mixture was vortexed for next 3 min, followed via an incubation period for 15 min at 80 °C. During the incubation period, tubes were intermittently tapped every 4 min. Subsequently, the tubes were centrifuged at 14,000 rpm for 15 min at room temperature to isolate the supernatant. The EX-tablet was then added in a quantity sufficient for 1.5–2.0 ml, and the mixture was centrifuged again at 15,000 g for 5 min. The procedure continued by

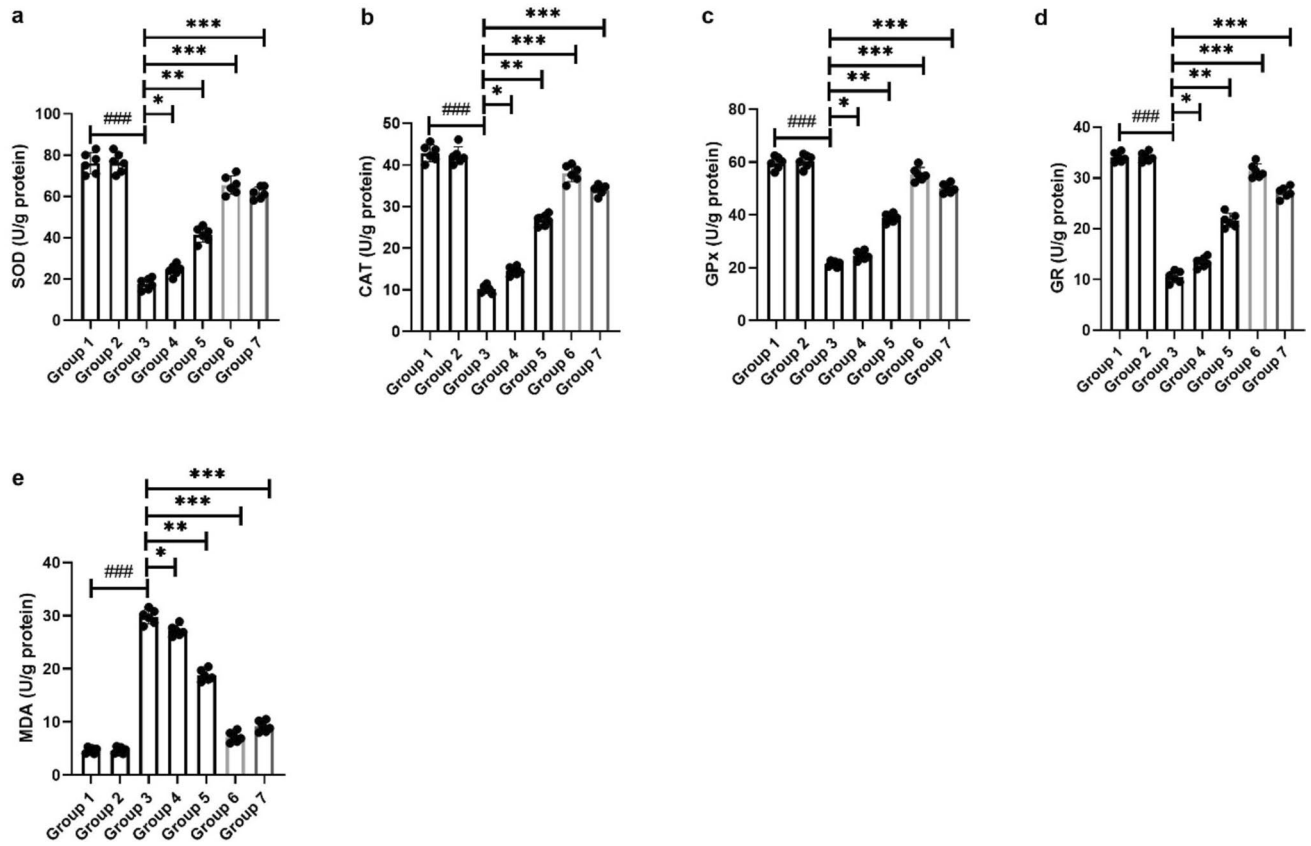

Fig. 4 Effect of sinomenine intake on antioxidant parameter against DSS-induced UC in rats. **a** SOD, **b** CAT, **c** GPx, **d** GR and **e** MDA. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

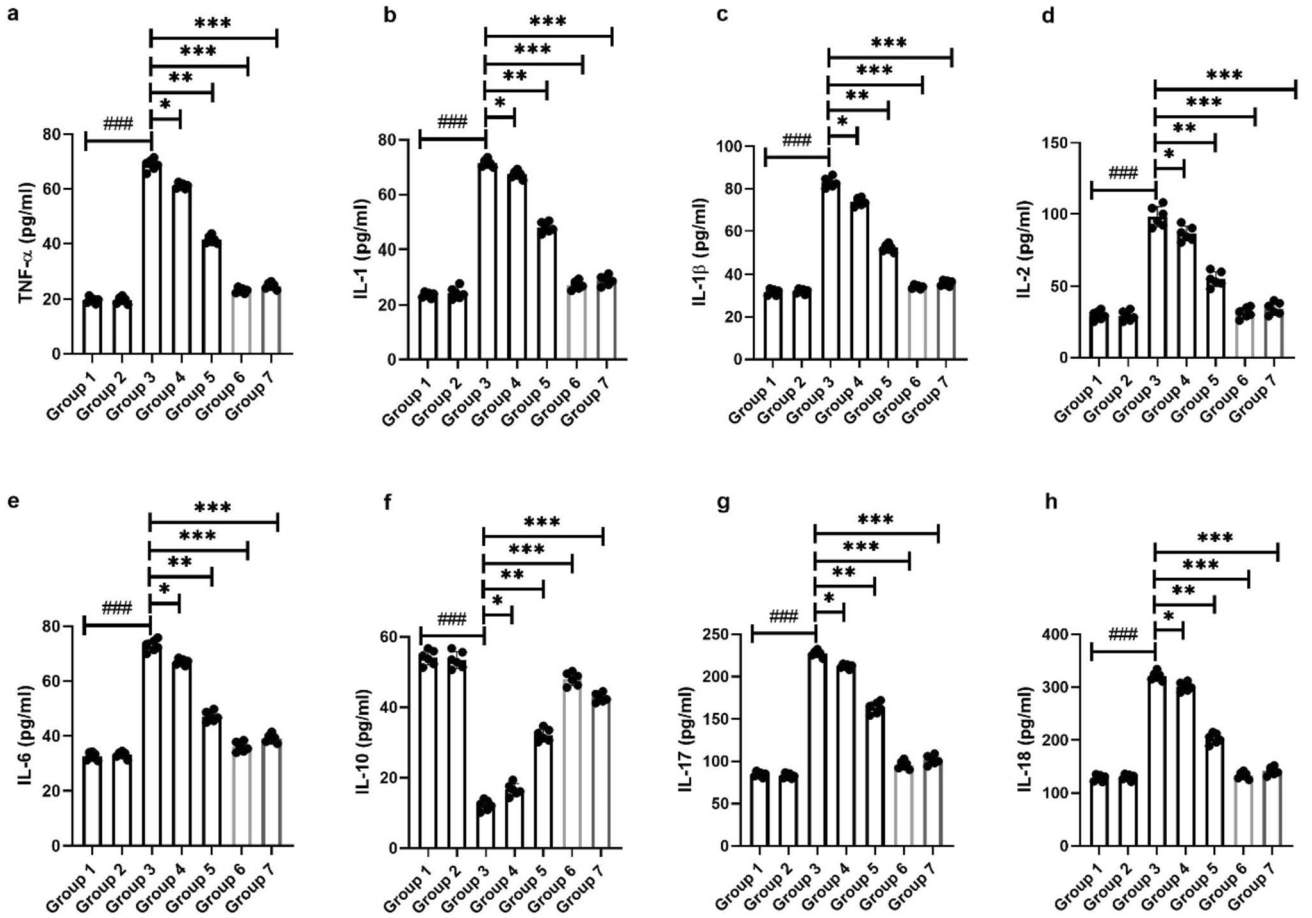

Fig. 5 Effect of sinomenine intake on cytokines level in serum against DSS-induced UC in rats. **a** TNF-α, **b** IL-1, **c** IL-1β, **d** IL-2, **e** IL-6, **f** IL-10, **g** IL-17, and **h** IL-18. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

adding 15 µl of proteinase K and AL buffer and incubated at 70 °C for 10 min. Following this, approximately 300 µl of absolute alcohol was added, and the mixture was centrifuged for 1 min at 12,000 rpm. Simultaneously, 500 µl of AW1 buffer was added to the column, and the entire setup was centrifuged at 14,000 rpm for 1 min. Nanodrop (Thermo Scientific, USA) was used to measure the DNA level. Agarose gel electrophoresis was used to check the size and integrity of the DNA. Samples with good integrity and levels were chosen for the next sequencing step. The primers 338F (5′-ACTCCTACGGGAGGCAGCA-3′) and 806R (5′-GGACTACHVGGGTWTCTAAT-3′) were used to amplify the DNA on a GeneAmp 9700 thermal cycler PCR system (Applied Biosystems, USA). The PCR amplicons were purified using the AxyPrep DNA Gel Extraction Kit (Axygen, USA), and the QuantiFluorTM-ST fluorometer (Promega, USA) was used to quantify them.

Statistical analysis

The mean ± standard error of the mean was used to show the data. One-way analysis of variance (ANOVA) and Dunnett's t test for multiple comparisons were used to find significant differences in the statistical analysis. GraphPad Prism 8.0 software was used for the statistical analysis, and a P value below 0.05 was taken as statistically significant.

Results

Body weight, disease activity index, colon length, spleen index, water and food intake

The body weight of the rats in the DSS group was lower than the others. This shows that the disease was induced. The body weight improved significantly with sinomenine

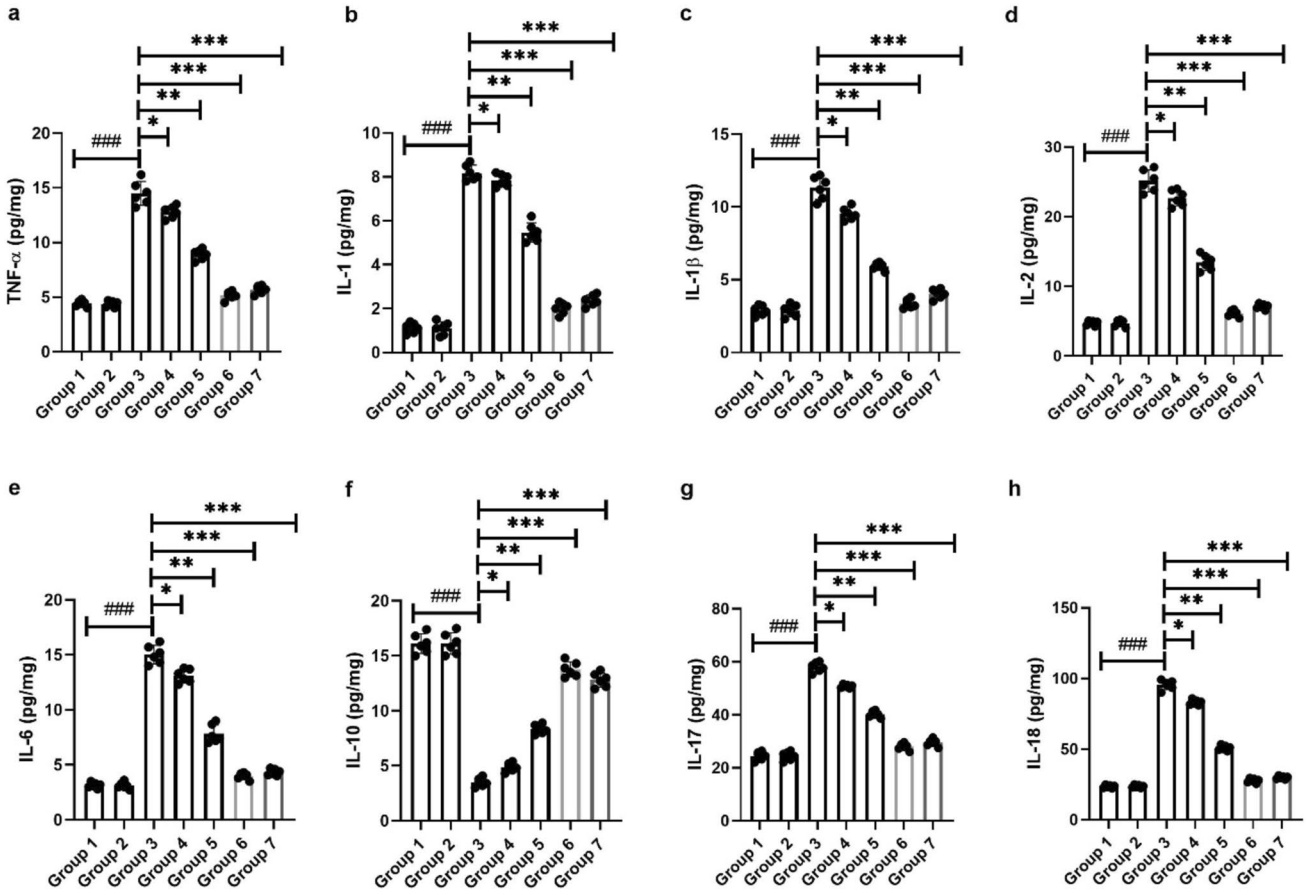

Fig. 6 Effect of sinomenine intake on cytokines level in stomach against DSS-induced UC in rats. **a** TNF-α, **b** IL-1, **c** IL-1β, **d** IL-2, **e** IL-6, **f** IL-10, **g** IL-17, and **h** IL-18. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

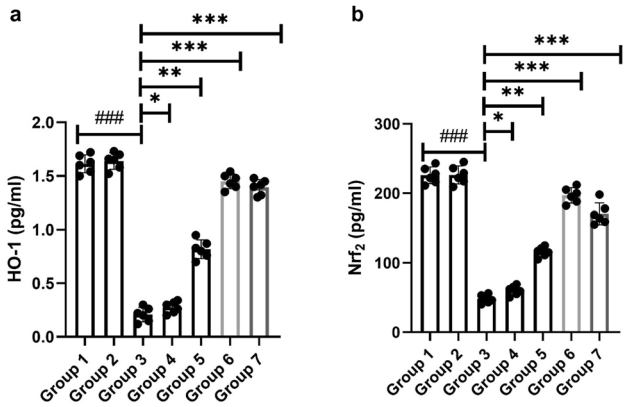

Fig. 7 Effect of sinomenine intake on HO-1 and Nrf_2 against DSS-induced UC in rats. **a** HO-1 and **b** Nrf_2. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

treatment (Fig. 1b). The normal rats had no DAI, but the DSS rats had a higher DAI index because of the disease. Dose dependently treatment of sinomenine remarkably ($P < 0.001$) reduced the DAI index (Fig. 1c). Figure 1d exhibited the colon length of all-group rats. DSS group rats demonstrated the decreased colon length and sinomenine treated rats showed the enhancement of colon. DSS group rats showed the increased spleen index (Fig. 1e) and sinomenine treatment significantly ($P < 0.001$) decreased the spleen index. DSS group rats exhibited the reduction in the average daily food intake (Fig. 1f), water intake (Fig. 1g) and sinomenine treatment remarkably restored the food and water intake at dose dependent manner.

NO and MPO

The rats in the DSS group exhibited an elevated level of NO (Fig. 2a) and MPO (Fig. 2b), indicating increased inflammation. Treatment with sinomenine significantly ($P < 0.001$)

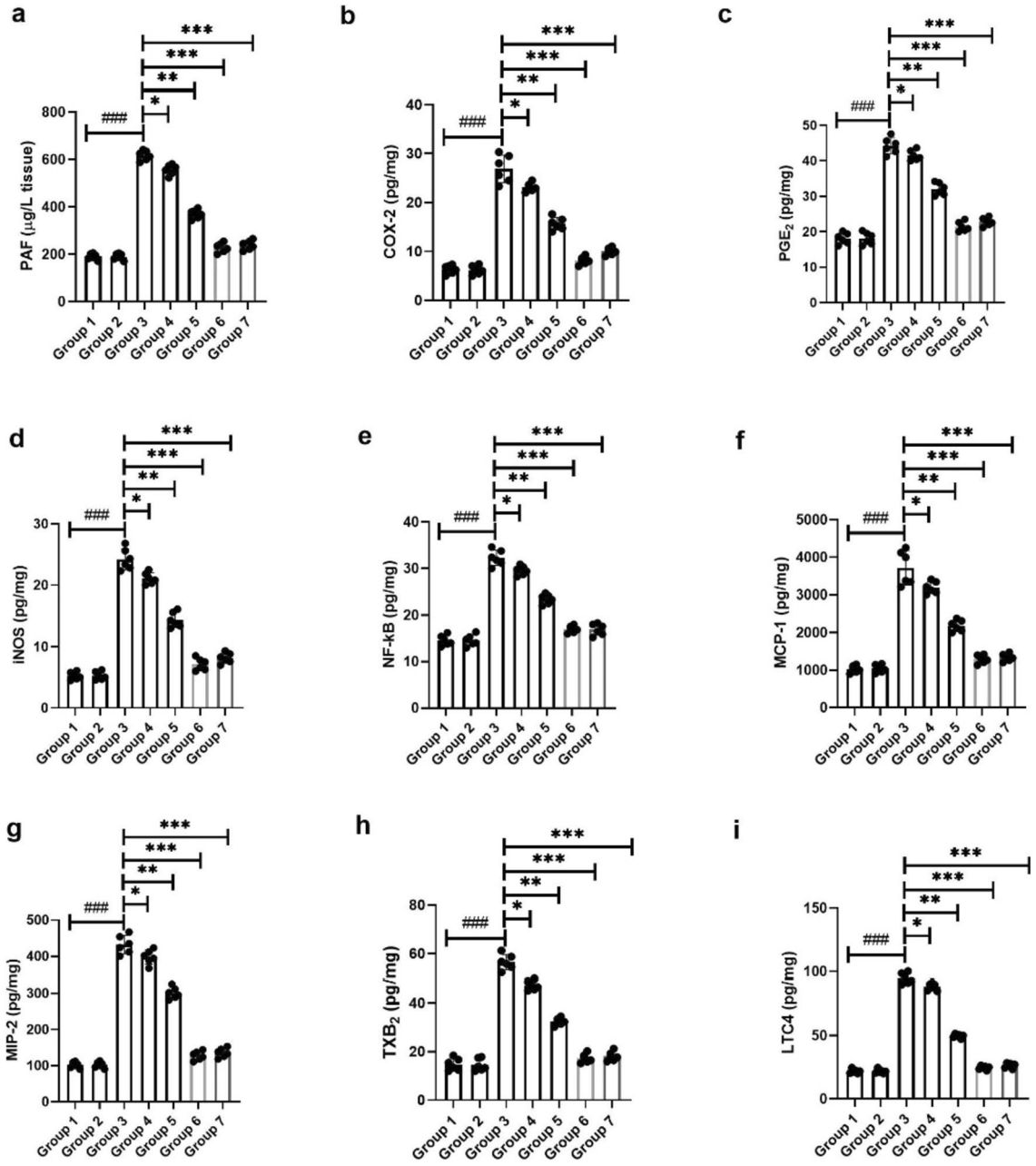

Fig. 8 Effect of sinomenine intake on inflammatory parameters in colon against DSS-induced UC in rats. **a** PAF, **b** COX-2, **c** PGE_2, **d** iNOS, **e** NF-κB, **f** MCP-1, **g** MIP-2, **h** TXB_2, and **i** LTC4. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

suppressed these levels, suggesting its anti-inflammatory effect.

ICAM-1 and VCAM-1

The level of ICAM-1 (Fig. 3a) and VCAM-1 (Fig. 3b) remarkably boosted in the DSS group rats and sinomenine treatment significantly ($P < 0.001$) suppressed the level.

Antioxidant parameters

The level of SOD (Fig. 4a), CAT (Fig. 4b), GPx (Fig. 4c), GR (Fig. 4d) was lower in the DSS group rats, and the level of MDA (Fig. 4e) was higher. Sinomenine treatment significantly improved the level of antioxidant parameters.

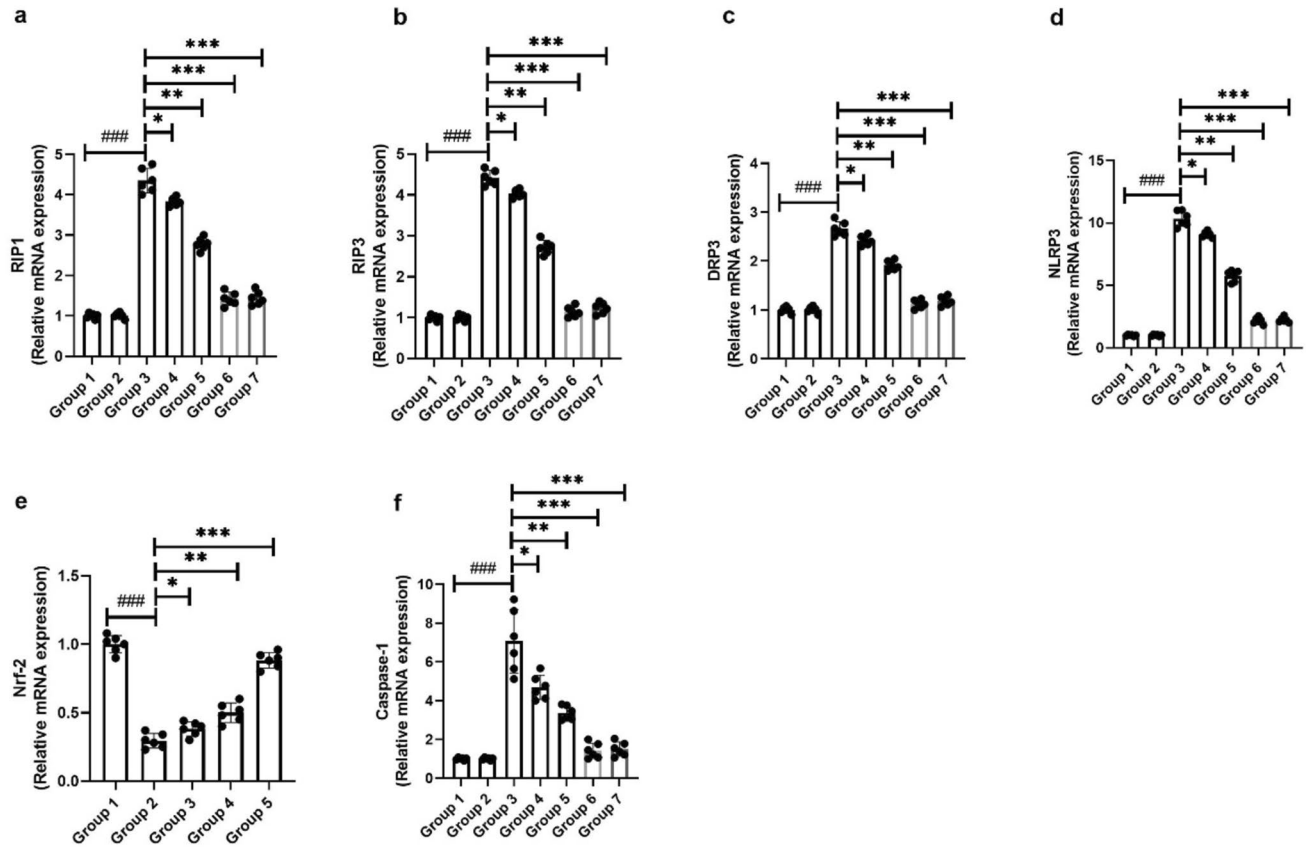

Fig. 9 Effect of sinomenine intake on mRNA expression against DSS-induced UC in rats. **a** RIP1, **b** RIP3, **c** DRP3, **d** NLRP3, **e** Nrf2, and **f** Caspase-3. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{###}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

Cytokines

Cytokines are important for the development of colorectal disease. The level of TNF-α (Fig. 5a), IL-1(Fig. 5b), IL-1β (Fig. 5c), IL-2 (Fig. 5d), IL-6 (Fig. 5e), IL-10 (Fig. 5f), IL-17 (Fig. 5g) and IL-18 (Fig. 5h) were changed in the DSS group rats, and sinomenine significantly changed the cytokines levels.

DSS group rats exhibited the altered level of TNF-α (Fig. 6a), IL-1(Fig. 6b), IL-1β (Fig. 6c), IL-2 (Fig. 6d), IL-6 (Fig. 6e), IL-10 (Fig. 6f), IL-17 (Fig. 6g), and IL-18 (Fig. 6h) in the colon tissue and sinomenine significantly changed the cytokines levels.

HO-1 and Nrf2

DSS-induced group rats exhibited the suppressed level of HO-1 (Fig. 7a), Nrf2 (Fig. 7b) and sinomenine treatment significantly ($P < 0.001$) improved the level.

Inflammatory and MMP parameters

DSS group rats exhibited the boosted level of PAF (Fig. 8a), COX-2 (Fig. 8b), PGE2 (Fig. 8c), iNOS (Fig. 8d), NF-κB (Fig. 8e), MCP-1 (Fig. 8f), MCP-2 (Fig. 8g), TXB2 (Fig. 8h), LCT4 (Fig. 8i), and sinomenine treatment significantly ($P < 0.001$) suppressed the inflammatory parameters level.

mRNA expression

DSS-induced group rats exhibited the altered level of mRNA expression such as RIP1 (Fig. 9a), RIP3 (Fig. 9b), DRP3 (Fig. 9c), NLRP3 (Fig. 9d), Nrf2 (Fig. 9e), caspase-1 (Fig. 9f) and sinomenine treatment remarkably restored the level suppressed the mRNA expression.

DSS-induced group rats demonstrated the altered level of mRNA expression viz., TNF-α (Fig. 10a), IL-1β (Fig. 10b), IL-6 (Fig. 10c), IL-18 (Fig. 10d), COX-2 (Fig. 10e), NF-κB (Fig. 10f) and sinomenine considerably restored the level of mRNA expression.

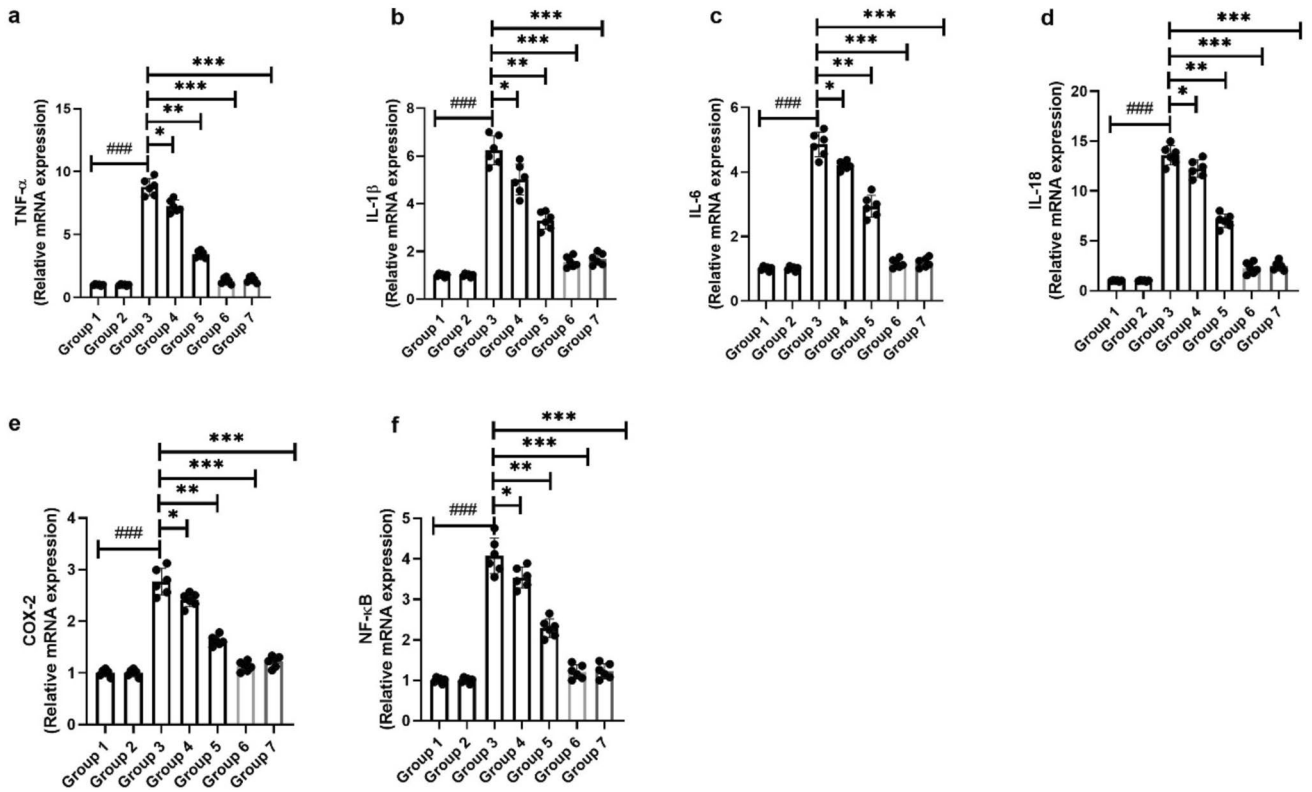

Fig. 10 Effect of sinomenine intake on mRNA expression against DSS-induced UC in rats. **a** TNF-α, **b** IL-1β, **c** IL-6, **d** IL-18, **e** COX-2 and **f** NF-κB. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{\#\#\#}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

Gut microbiota

The relative abundance of bacteria at phylum level was changed in the rats with DSS-induced colitis (Fig. 10a). DSS group demonstrated the altered level of firmicutes (Fig. 10b), Bacteroidetes (Fig. 10c), F/B ratio (Fig. 10d), Verrucomicrobia (Fig. 10e), Actinobacteria (Fig. 10f) and sinomenine remarkably restored the level of relative abundance of gut microbiota at phylum level.

Figure 11a showed the altered relative abundance at genus level of all-group rats. DSS-induced group rats showed the Bacteroides (Fig. 11b), Lactobacillus (Fig. 11c), norank_f_ Muribaculanceae (Fig. 11d), Romboustsia (Fig. 11e), Akkermansia (Fig. 11f), and sinomenine significantly restore the relative abundance of gut microbiota.

Discussion

The main types of IBD are Crohn's disease and ulcerative colitis, which affect millions of people around the world. These conditions cause long-term, uncontrolled inflammation of the lining of the intestines (Dutra et al. 2011). UC is a digestive tract disease categorized via chronic inflammation and ulceration of submucosa and colonic mucosa (Gao et al. 2019). The clinical manifestations of UC such as diarrhoea, sputum, pus and bloody stools, abdominal pain, and ulcerative colitis are recurring chronic conditions that can manifest at any age and affect both males and females (Da Silva et al. 2014). They are more prevalent among individuals in the young and middle-aged demographic, particularly in developed Western countries (Gao et al. 2019). Current immunosuppressive, sulphonamides and hormones agents were used for the treatment of UC, these treatment only control the UC symptoms, but it induces the side effects and hormones resistance (Gao et al. 2019). Recently, plant-based drug is gaining more popularity due to potential effect against UC (Liu et al. 2021; Patel et al. 2022). The purpose of this study was to examine how sinomenine protects against UC caused by DSS and to uncover the processes behind this protection (Fig. 12).

Various chemicals have been utilized to induce experimental ulcerative colitis (UC) in research studies. These include DSS, 2,4,6-trinitrobenzene sulfonic acid (TNBS), acetic acid, and oxazolone. These agents are employed to replicate and study the inflammatory processes associated

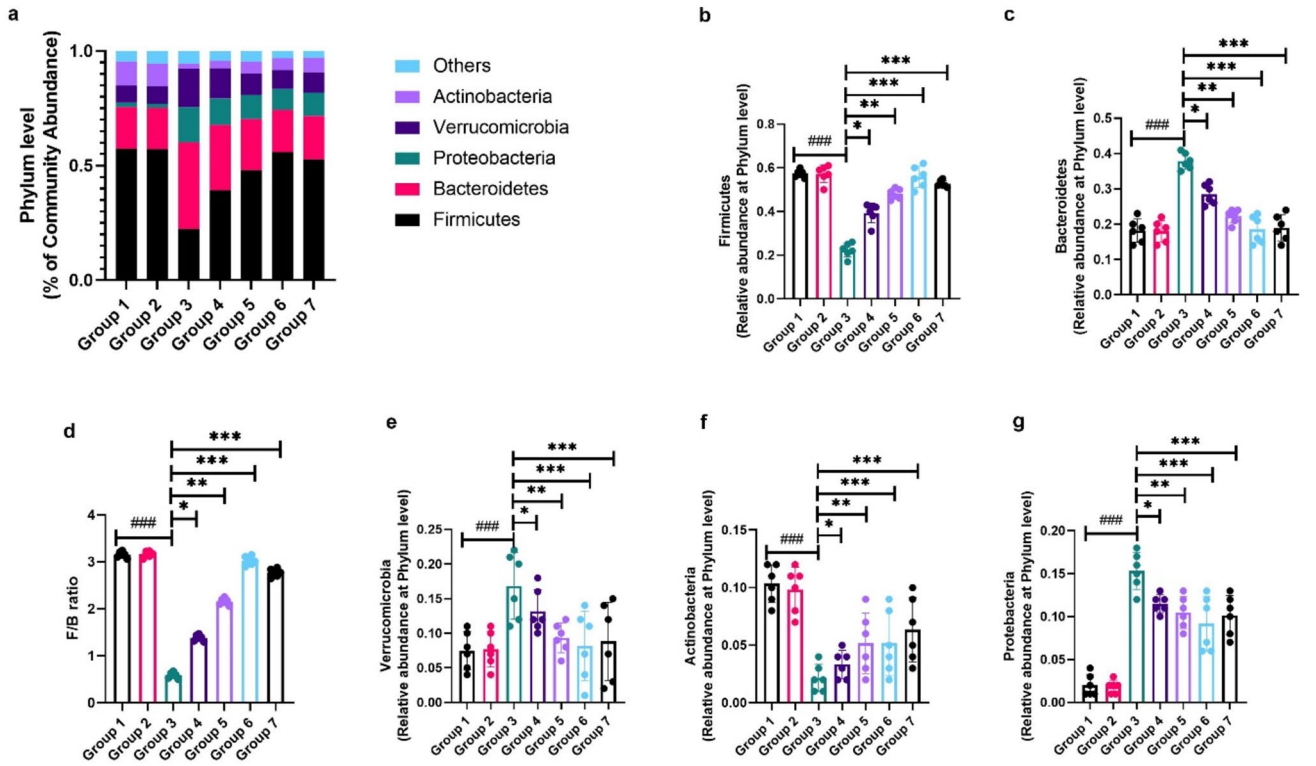

Fig. 11 Effect of sinomenine intake on relative abundance of gut microbiota at phylum level against DSS-induced UC in rats. **a** microbiota at phylum level, **b** Relative abundance of Firmicutes, **c** Relative abundance of Bacteroidetes, **d** F/B ratio, **e** Relative abundance of Verrucomicrobia, **f** Relative abundance of Actinobacteria and **g** Relative abundance of Protebacteria. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{\#\#\#}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

with UC under controlled laboratory conditions (Min et al. 2021). Among all the chemical-induced models, DSS-induced UC model gets more popularity due to similar pathologic feature and clinical symptoms to those of human IBD (Perše and Cerar 2012; Low et al. 2013). UC induces the UC in 2 phases, first phase, the rodent had weight loss, hair erect, bloody stool and diarrhea; second, it exhibited the alteration in the crypt structure, mucin depletion, infiltration of inflammatory cells, and epithelial cell alterations (Min et al. 2021). DSS control rats revealed in the reduction of body weight, colon weight, colon length, spleen index, and enhanced DAI score. The histopathology exhibited the reduction in the mucin, degeneration epithelial and infiltration of inflammatory cells. These results suggest the successfully establishment of UC model and Sinomenine remarkably restore the clinical manifestations and histopathology.

Certainly, it is well-established that both MAPK and NF-κB signaling pathways play pivotal roles in the regulation of inflammation. Activation of these signaling molecules leads to the induction and secretion of numerous inflammatory cytokines, contributing to the intricate network of inflammatory responses in various conditions, including ulcerative colitis. The crosstalk and interplay between MAPKs and NF-κB represent a complex regulatory system that influences the inflammatory cascade, and understanding these mechanisms is crucial for developing targeted interventions and treatments for inflammatory diseases. The overproduction of inflammatory cytokines has been confirmed to be related to expansion of UC. DSS remarkably induces an enhance the production of inflammatory cytokines in both distal and mild colons; among the cytokines, TNF-α is responsible for the activation of inflammatory reaction via infiltration of lymphocytes and induces the injury in the colon tissue (Patel et al. 2022). TNF-α is a key cytokine in inflammatory diseases such as IBD (CD and UC). It can stimulate the intestinal immune cells, monocytes and macrophages, and induce them to secrete other cytokines that amplify the inflammatory response. In the pathologic development of colitis, cytokines such as IL-1, IL-17, and TNF-α cause inflammatory cascades and tissue damage (Badr et al. 2020). Sinomenine significantly modulated the cytokine levels in DSS-induced UC by inhibiting inflammatory mediators. This indicated the anti-inflammatory potential of SIN through attenuating various components of

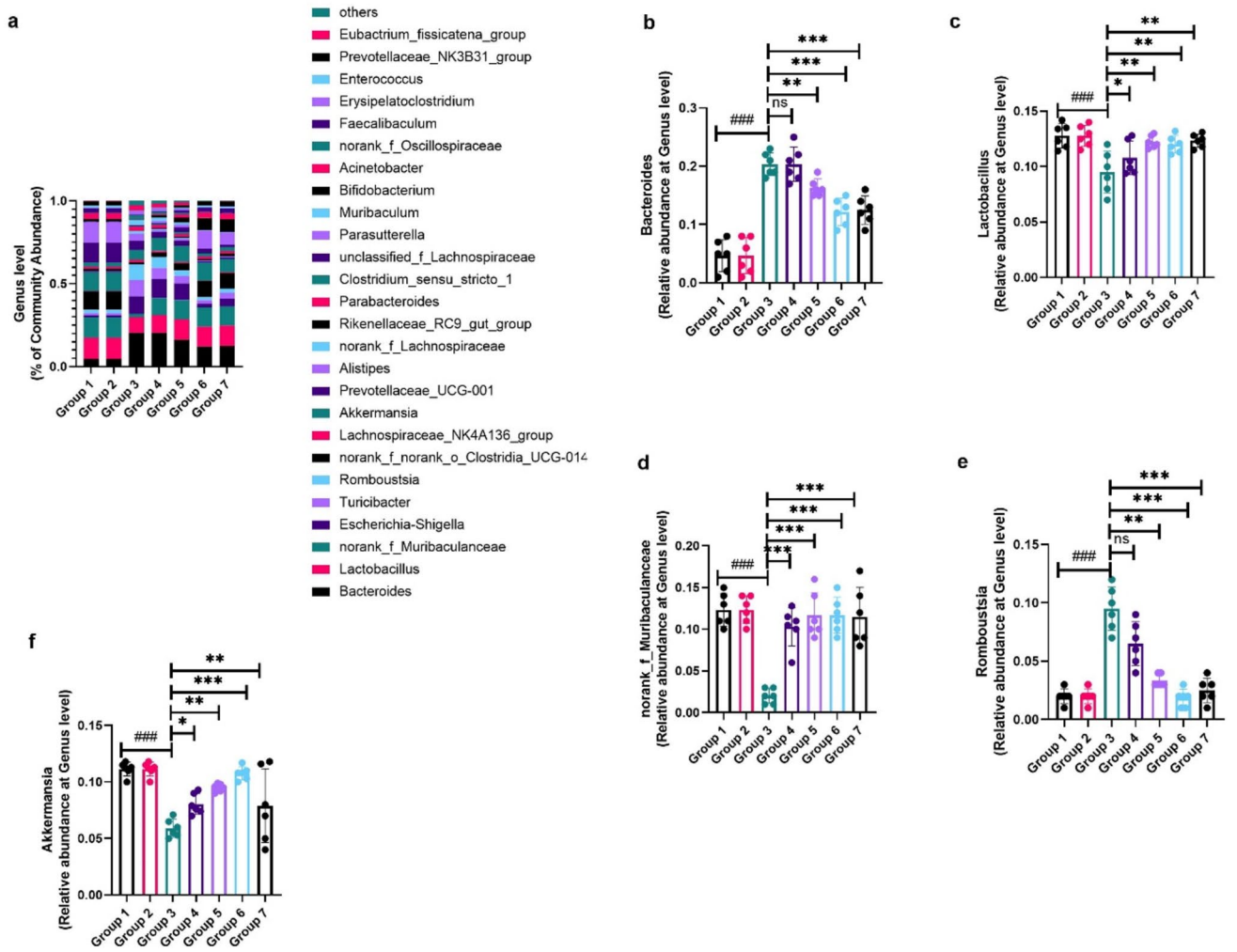

Fig. 12 Effect of sinomenine intake on relative abundance of gut microbiota at genus level against DSS-induced UC in rats. **a** microbiota at genus level, **b** Relative abundance of Bacteroides, **c** Relative abundance of Lactobacillus, **d** Relative abundance of norank_f_Muribaculanceae, **e** Relative abundance of Romboustsia and **f** Relative abundance of Akkermansia. Values are expressed as mean ± SEM ($n = 6$/group). The UC group rats compared with normal control and consider significant ($^{\#\#\#}P < 0.001$) and sinomenine group rats compared with the UC group rats ($^{*}P < 0.05$ consider as significant, $^{**}P < 0.01$ consider as more significant and $^{***}P < 0.001$ consider as extreme significant)

the immune response, such as intracellular calcium, IL-10, IL-6, NO, MCP-1, MCP-3, GM-CSF, MIP (MIP-1α and MIP-1β) and LIF, a member of the IL-6 family. To explore the mechanism of SIN's cytokine suppression, we assessed the impact of SIN on the MAPK and NF-κB pathways. As anticipated, SIN treatment reduced the MAPK and NF-κB levels. Since MAPK and NF-κB are key factors in UC development, the result demonstrated that SIN treatment effectively inhibited the MAPK and NF-κB activation, suggesting a protective role against UC.DSS has the ability to permeate the mucosal membrane of the intestine. Within the lamina propria of the colon mucosa, macrophages containing DSS molecules can be observed, subsequently infiltrating inflammatory cells (Min et al. 2021). When DSS stimulates the intestinal surface, it activates macrophages to secrete inflammatory cytokines, which contribute to the development of UC. The macrophages produce two enzymes, iNOS and COX-2, that are important for the release of inflammatory cytokines (Sakthivel and Guruvayoorappan 2013). IL-10 is a cytokine with a strong anti-inflammatory effect and its level is reduced in UC, leading to increased inflammation. MPO is an enzyme released by neutrophils and changes in its activity in the colon can indicate the degree of neutrophil infiltration. MPO consider as the biomarker for colon

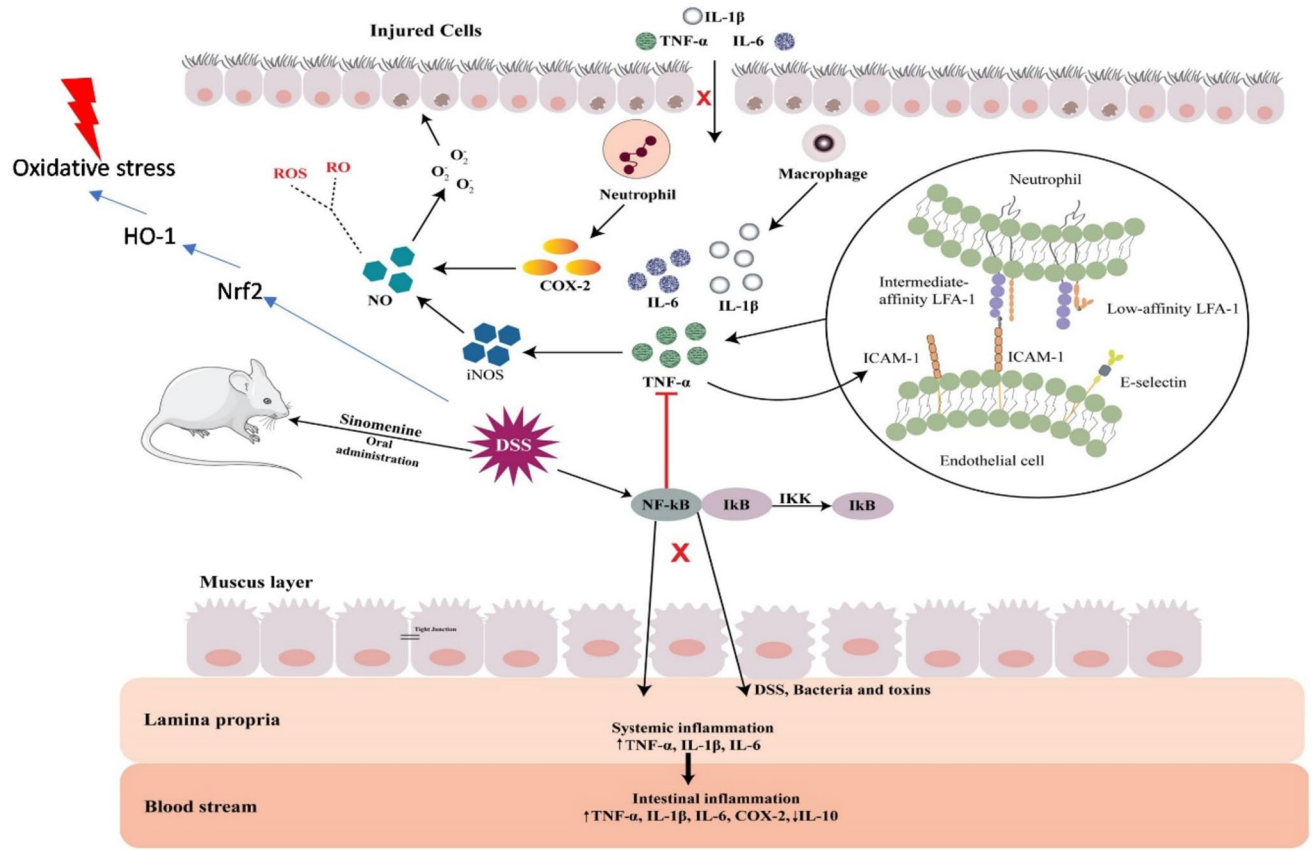

Fig. 13 Shows the underlying mechanism of sinomenine against the DSS-induced ulcerative colitis

diseases such as UC and enhanced activity of MPO was completed suppressed via Sinomenine which can suggest the protective effect against UC.

PPARγ is an important nuclear receptor that regulates the expression of genes involved in many diseases, such as colitis (Yuan et al. 2015). PPARγ is an anti-inflammatory factor that reduces experimental colitis when overexpressed. On the other hand, blocking PPARγ increases the susceptibility to colitis (Cao et al. 2018). By negatively regulating various transcription factors, PPARγ reduces intestinal inflammation. PPARγ's anti-UC effects are mediated by the NF-κB pathway. It has been reported that PPARγ can bind to NF-κB p65 and promote its exit from the nucleus, thus blocking NF-κB-mediated transcription. Moreover, research indicates that PPARγ activation lowers NF-κB activation triggered by DSS and inhibits cytokine production (Cao et al. 2018).

The NLRP3 inflammasome is an immune system component that contributes to UC development. It is a protein complex that activates Caspase-1 when stimulated, leading to the release and processing of IL-1β. Unlike other cytokines, IL-1β secretion requires inflammasome activation (Cao et al. 2018). The NLRP3 inflammasome is a protein complex that regulates the innate immune system. It consists of NLRP3 (a NOD-like receptor with a pyrin domain), ASC (an adaptor protein with a caspase recruitment domain), and pro-caspase-1 (an inactive form of caspase-1) (Ali et al. 2023). The NLRP3 inflammasome activates caspase-1 by cutting pro-caspase-1, which then cuts pro-IL-1β and pro-IL-18 into their active forms. These cytokines are powerful inflammation inducers. The NLRP3 inflammasome is involved in the abnormal inflammatory response in the colon. Some studies have indicated that more NLRP3 inflammasome activation may cause persistent inflammation in UC patients (Itani et al. 2016; Ali et al. 2023; Sun and Zhu 2023). NLRP3 activation in UC is unclear, but may involve microbial imbalance, epithelial damage, and genetic factors. Activated-NLRP3 inflammasome causes pro-inflammatory cytokines, especially IL-1β and IL-18, to be released, which worsen the colon inflammation (Cao et al. 2020; Ali et al. 2023; Xu et al. 2023).

IBD development is strongly influenced by gut microbiota imbalance, which is widely recognized (Nascimento et al. 2020; Fu et al. 2022). IBD patients have less beneficial and commensal fecal bacteria, such as Firmicutes. Some Firmicutes, like Clostridium sensu stricto, Prevollaceae, and Oscillospiraceae, make butyrate from their fermentable carbon sources (He et al. 2022). Patients suffer from the inflammatory bowel disease (IBD) exhibit an increased

abundance of Bacteroidota, particularly associated with unclassified Bacteroides and Bacteroides acidifaciens (Gagnière et al. 2016; He et al. 2022). The degradation of mucin, a colon-protecting substance made by epithelial cells, and the production of succinic acid and acetic acid, which can cause inflammation in colitis, are characteristics of Bacteroides acidifaciens. This bacterium is involved in worsening and advancing colitis (He et al. 2022). Rikenellaceae RC9, a member of the Rikenellaceae family in the Bacteroidota phylum, is significantly associated with systemic inflammatory cytokines (Cai et al. 2021). Lactobacilli, which are harmless and beneficial bacteria in the gut, can act as probiotics that regulate the host's immune system. They do this by strengthening the connections between epithelial cells and affecting the levels of cytokines that cause or reduce inflammation (Corthésy et al. 2007; Mazziotta et al. 2023). We also observed the reduced-relative abundance of Actinobacteriota and Verrucomicrobiota.

Conclusion

By affecting different molecular pathways and gut microbes, sinomenine helped rats with ulcerative colitis heal their inflamed and damaged colon tissues. Sinomenine lowered the levels of inflammation, oxidative stress, and cell death, and increased the levels of factors that protect and repair the cells. Sinomenine also altered the gut bacteria balance, boosting the good ones and reducing the bad ones. These findings indicate that sinomenine could be a promising treatment for ulcerative colitis (Fig. 13).

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

Declarations

Competing interests All the authors declare none conflict of interest.

Ethics approval This study has been approved by the Ethics Committee of Jinan Central Hospital (AF/SC-04/09.0).

References

Ali FEM, Ibrahim IM, Ghogar OM et al (2023) Therapeutic interventions target the NLRP3 inflammasome in ulcerative colitis: comprehensive study. World J Gastroenterol 29:1026–1053

Badr G, Elsawy H, Malki MA et al (2020) Protective effects of myristicin against ulcerative colitis induced by acetic acid in male mice. Food Agric Immunol 31:435–446. https://doi.org/10.1080/09540105.2020.1739626

Bai D, Du J, Bu X et al (2021) ALDOA maintains NLRP3 inflammasome activation by controlling AMPK activation. Autophagy. https://doi.org/10.1080/15548627.2021.1997051

Biasizzo M, Kopitar-Jerala N (2020) Interplay Between NLRP3 Inflammasome and Autophagy. Front Immunol 11:78

Cai B, Pan J, Chen H et al (2021) Oyster polysaccharides ameliorate intestinal mucositis and improve metabolism in 5-fluorouracil-treated S180 tumour-bearing mice. Carbohydr Polym. https://doi.org/10.1016/j.carbpol.2020.117545

Cao H, Liu J, Shen P et al (2018) Protective Effect of Naringin on DSS-Induced Ulcerative Colitis in Mice. J Agric Food Chem 66:13133–13140. https://doi.org/10.1021/acs.jafc.8b03942

Cao R, Ma Y, Li S et al (2020) 1,25(OH)2D3 alleviates DSS-induced ulcerative colitis via inhibiting NLRP3 inflammasome activation. J Leukoc Biol 108:283–295. https://doi.org/10.1002/JLB.3MA0320-406RR

Corthésy B, Gaskins HR, Mercenier A (2007) Cross-talk between probiotic bacteria and the host immune system. J Nutr 137:7815

Da Silva BC, Lyra AC, Rocha R, Santana GO (2014) Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. World J Gastroenterol 20:9458–9467

de Nascimento R, P do, Machado AP da F, Galvez J, et al (2020) Ulcerative colitis: Gut microbiota, immunopathogenesis and application of natural products in animal models. Life Sci 258:7345

Dutra RC, Claudino RF, Bento AF et al (2011) Preventive and therapeutic euphol treatment attenuates experimental colitis in mice. PLoS ONE. https://doi.org/10.1371/journal.pone.0027122

Fu R, Wang L, Meng Y et al (2022) Apigenin remodels the gut microbiota to ameliorate ulcerative colitis. Front Nutr. https://doi.org/10.3389/fnut.2022.1062961

Gagnière J, Raisch J, Veziant J et al (2016) Gut microbiota imbalance and colorectal cancer. World J Gastroenterol 22:501–518

Gao W, Wang C, Yu L et al (2019) Chlorogenic acid attenuates dextran sodium sulfate-induced ulcerative colitis in mice through MAPK/ERK/JNK Pathway. Biomed Res Int. https://doi.org/10.1155/2019/6769789

Gao Y, Zhou B, Zhang H et al (2022) L-Ergothioneine exhibits protective effects against dextran sulfate sodium-induced colitis in mice. ACS Omega 7:21554–21565. https://doi.org/10.1021/acsomega.2c01350

He C, Gao M, Zhang X et al (2022) The protective effect of sulforaphane on dextran sulfate sodium-induced colitis depends on gut microbial and Nrf2-Related Mechanism. Front Nutr. https://doi.org/10.3389/fnut.2022.893344

Il KT (2015) The role of barrier dysfunction and change of claudin expression in inflammatory bowel disease. Gut Liver 9:699–700

Itani S, Watanabe T, Nadatani Y et al (2016) NLRP3 inflammasome has a protective effect against oxazolone-induced colitis: A possible role in ulcerative colitis. Sci Rep. https://doi.org/10.1038/srep39075

Kihara N, De La Fuente SG, Fujino K et al (2003) Vanilloid receptor-1 containing primary sensory neurones mediate dextran sulphate sodium induced colitis in rats. Gut 52:713–719. https://doi.org/10.1136/gut.52.5.713

Kim MJ, Yoon JH, Ryu JH (2016) Mitophagy: A balance regulator of NLRP3 inflammasome activation. BMB Rep 49:529–535. https://doi.org/10.5483/BMBRep.2016.49.10.115

Li L, Fang P, Chen J et al (2021) Protective effect of sinomenine on isoproterenol-induced cardiac hypertrophy in mice. J Appl Biomed 19:142–148. https://doi.org/10.32725/jab.2021.014

Li Y, Cai W, Ai Z et al (2023) Protective effects of sinomenine hydrochloride on lead-induced oxidative stress, inflammation, and

apoptosis in mouse liver. Environ Sci Pollut Res 30:7510–7521. https://doi.org/10.1007/s11356-022-22386-1
Liu D, Huo X, Gao L et al (2018) NF-κB and Nrf2 pathways contribute to the protective effect of Licochalcone A on dextran sulphate sodium-induced ulcerative colitis in mice. Biomed Pharmacother 102:922–929. https://doi.org/10.1016/j.biopha.2018.03.130
Liu Y, Fang H, Liu H et al (2021) Goji berry juice fermented by probiotics attenuates dextran sodium sulfate-induced ulcerative colitis in mice. J Funct Foods. https://doi.org/10.1016/j.jff.2021.104491
Low D, Nguyen DD, Mizoguchi E (2013) Animal models of ulcerative colitis and their application in drug research. Drug Des Devel Ther 7:1341–1356
Lu C, Guo X, He X et al (2022) Cardioprotective effects of sinomenine in myocardial ischemia/reperfusion injury in a rat model. Saudi Pharm J 30:669–678. https://doi.org/10.1016/j.jsps.2022.04.005
Mahmoud TN, El-Maadawy WH, Kandil ZA et al (2021) Canna x generalis L.H. Bailey rhizome extract ameliorates dextran sulfate sodium-induced colitis via modulating intestinal mucosal dysfunction, oxidative stress, inflammation, and TLR4/ NF-κB and NLRP3 inflammasome pathways. J Ethnopharmacol. https://doi.org/10.1016/j.jep.2020.113670
Mazziotta C, Tognon M, Martini F et al (2023) Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. Cells 12:8
Min X, Guo Y, Zhou Y (2021) Protection against dextran sulfate sodium-induced ulcerative colitis in mice by neferine, a natural product from nelumbo nucifera gaertn. Cell J 22:523–531. https://doi.org/10.22074/cellj.2021.6918
Miranda KM, Espey MG, Wink DA (2001) A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric Oxide - Biol Chem 5:62–71. https://doi.org/10.1006/niox.2000.0319
Morsy MA, Gupta S, Nair AB et al (2019) Protective effect of spirulina platensis extract against dextran-sulfate-sodium-induced ulcerative colitis in rats. Nutrients. https://doi.org/10.3390/nu11102309
Okayasu I, Hatakeyama S, Yamada M et al (1990) A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. Gastroenterology 98:694–702. https://doi.org/10.1016/0016-5085(90)90290-H
Patel JI, Kumbhani M, Raval MM (2022) Protective effect of nelumbo nucifera plant on dextran sodium sulfate-induced ulcerative colitis in rats. Ann Natl Acad Med Sci 58:078–086. https://doi.org/10.1055/s-0042-1743133
Peng S, Shen L, Yu X et al (2023) The role of Nrf2 in the pathogenesis and treatment of ulcerative colitis. Front Immunol 14:6
Perše M (2012) Cerar A (2012) Dextran sodium sulphate colitis mouse model: Traps and tricks. J Biomed Biotechnol 78:7
Qu X, Li Q, Song Y et al (2020) Potential of myricetin to restore the immune balance in dextran sulfate sodium-induced acute murine ulcerative colitis. J Pharm Pharmacol 72:92–100. https://doi.org/10.1111/jphp.13197
Sakthivel KM, Guruvayoorappan C (2013) Amentoflavone inhibits iNOS, COX-2 expression and modulates cytokine profile, NF-κB signal transduction pathways in rats with ulcerative colitis. Int Immunopharmacol 17:907–916. https://doi.org/10.1016/j.intimp.2013.09.022
Sun H, Zhu Y (2023) Progress on Regulation of NLRP3 Inflammasome by Chinese Medicine in Treatment of Ulcerative Colitis. Chin J Integr Med 29:750–760
Xu LF, Teng X, Guo J, Sun M (2012) Protective effect of intestinal trefoil factor on injury of intestinal epithelial tight junction induced by platelet activating factor. Inflammation 35:308–315. https://doi.org/10.1007/s10753-011-9320-x
Xu H, Chen J, Chen P et al (2023) Costunolide covalently targets NACHT domain of NLRP3 to inhibit inflammasome activation and alleviate NLRP3-driven inflammatory diseases. Acta Pharm Sin B 13:678–693. https://doi.org/10.1016/j.apsb.2022.09.014
Yu T, Lu X, Liang Y et al (2023) Ononin alleviates DSS-induced colitis through inhibiting NLRP3 inflammasome via triggering mitophagy. Immunity, Inflamm Dis 11:56. https://doi.org/10.1002/iid3.776
Yuan G, Chen X, Li D (2015) Modulation of peroxisome proliferator-activated receptor gamma (PPAR γ) by conjugated fatty acid in obesity and inflammatory bowel disease. J Agric Food Chem 63:1883–1895. https://doi.org/10.1021/jf505050c
Yuan Y, Zhang Y, He X, Fan S (2018) Protective effects of sinomenine on CFA-induced inflammatory pain in rats. Med Sci Monit 24:2018–2024. https://doi.org/10.12659/MSM.906726
Zhang J, Hu R, Xia ZK et al (2012) Protective effects of sinomenine against doxorubicin-induced nephrosis in rats. J Asian Nat Prod Res 14:678–687. https://doi.org/10.1080/10286020.2012.685070
Zhao J, Hong T, Dong M et al (2013) Protective effect of myricetin in dextran sulphate sodium-induced murine ulcerative colitis. Mol Med Rep 7:565–570. https://doi.org/10.3892/mmr.2012.1225
Zhou T, Cai Z, Sun Y, Lv M (2020) Protective effect of sinomenine on zymosan-induced acute peritonitis in mice. Lat Am J Pharm 39:170–176