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RESEARCH

Umbelliprenin attenuates comorbid behavioral disorders in acetic acid-induced colitis in mice: mechanistic insights into hippocampal oxidative stress and neuroinflammation

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Abstract
Inflammatory bowel disease (IBD) is often accompanied by psychiatric disorders. Emerging evidence suggests that neuroinflammation and oxidative stress contribute to the psychiatric symptoms associated with IBD. Umbelliprenin (UMB) possesses several pharmacological properties, including anti-inflammatory and antioxidant effects. This study aimed to investigate the protective effects of UMB on comorbid behavioral disorders in a mouse model of experimental colitis, focusing on its potential anti-neuroinflammatory and antioxidant activities. After inducing colitis with acetic acid, male NMRI mice were treated for 7 consecutive days with UMB, saline, or dexamethasone. Behavioral assessments included the forced swimming test (FST), splash test, open field test (OFT), and elevated plus maze (EPM). Histopathological changes in the colon were evaluated, and total antioxidant capacity (TAC), malondialdehyde (MDA) levels, and the expression of inflammatory genes (TNFα, IL1β, and TLR4) were measured in the hippocampus. Colitis was associated with increased immobility time in the FST, reduced entries and time spent in the open arms of the EPM, decreased grooming behavior in the splash test, and reduced time spent in the central zone of the OFT. Colitis also resulted in a reduction in TAC and an increase in MDA levels and inflammatory gene expression in the hippocampus. UMB treatment mitigated the behavioral disorders associated with colitis, reduced neuroinflammation and oxidative stress in the hippocampus, and alleviated histopathological alterations in the colon. In conclusion, UMB may reduce behavioral disorders induced by colitis by decreasing oxidative stress and neuroinflammation in the hippocampus.

Keywords Colitis · Behavioral disorders · Umbelliprenin · Oxidative stress · Neuroinflammation

Introduction

Inflammatory bowel disease (IBD) is a chronic and relapsing gastrointestinal disorder that manifests primarily in two forms: Crohn's disease (CD) and ulcerative colitis (UC) (Khan et al. 2019). The intestinal epithelial layer serves as the first line of mucosal defense in the gut (Hamouda et al. 2011; Bruwer et al. 2001). Epithelial cells express toll-like receptors (TLRs) to detect antigens within the intestinal lumen (Kobayashi et al. 2005). The activation of these receptors in IBD triggers the release of inflammatory cytokines, including TNF-α and IL-1β (Bakiri et al. 2015; Putoczki et al. 2013; Zhang et al. 2015; Awasthi et al. 2017; Orazi et al. 1996; Shin et al. 2012). Oxidative stress has also been implicated in the pathogenesis of IBD (Bourgonje et al. 2020). Previous studies have shown that reducing oxidative stress can alleviate the severity of IBD (Jeon et al. 2020; Zhao et al. 2021).

Researchers have identified a significant association between gut and brain functions, referred to as the Brain-Gut Axis (Bastiaanssen et al. 2023). Numerous experimental and clinical studies have confirmed that IBD is linked to behavioral disorders (Thavamani et al. 2023; Qian et al. 2023). However, the specific mechanisms underlying this association are not fully understood.

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Emerging studies suggest that the inflammatory response plays a critical role in the pathophysiology of behavioral disorders, with a connection between neuroinflammation and psychiatric conditions such as depression and anxiety (Hassamal 2023; Guo et al. 2023; Islam et al. 2023). Preclinical evidence indicates that increased production of inflammatory cytokines in certain brain regions, such as the hippocampus, is associated with anxiety- and depression-like behaviors (Arabi et al. 2021; Mazrooei et al. 2023; Amini-Khoei et al. 2019). Furthermore, there is a well-established direct relationship between oxidative stress and the development of psychiatric disorders (Correia et al. 2023). Markers of oxidative stress, such as malondialdehyde (MDA), are elevated in the serum of patients with psychiatric disorders (Luan et al. 2018; Alvarez-Mon et al. 2022). Nitrite levels are also directly correlated with the severity of behavioral disorders (García et al. 2011). Previous studies have demonstrated that reducing nitrite levels can mediate the antidepressant and anxiolytic effects of certain agents (Omidi-Ardali et al. 2020; Lorigooini et al. 2021; Walia et al. 2019). Additionally, it has been shown that total antioxidant capacity (TAC) decreases following the onset of psychiatric disorders (Hashemi et al. 2017; Daneshzad et al. 2020). An inverse relationship between nutritional TAC and the likelihood of depression and anxiety in adults has been reported (Milajerdi et al. 2019).

Coumarins, which are natural benzopyrene derivatives, are abundant in many plants and exhibit a wide range of pharmacological properties (Iranshahi et al. 2009; Shakeri et al. 2014). Umbelliprenin (UMB), a sesquiterpene coumarin derived from the Ferula species, has been shown to possess various biological activities, including neuroprotective, antioxidative, proapoptotic, and anti-inflammatory effects (Hashemzaei et al. 2015; Iranshahi et al. 2009; Shahraki et al. 2020). Studies have demonstrated that UMB exerts neuroprotective effects in a model of neuropathic pain by alleviating oxidative stress (Shahraki et al. 2020). Additionally, UMB has been reported to have anti-inflammatory properties (Khaghanzadeh et al. 2017). It has also been shown that UMB mitigates autism-related behaviors in mice by reducing oxidative stress and increasing methyl CpG binding protein 2 (MECP2) levels (Karimi et al. 2023).

This study aimed to evaluate the protective effects of UMB on comorbid behavioral disorders in a mouse model of acetic acid-induced colitis, with a focus on its potential anti-neuroinflammatory and antioxidant effects.

Materials and methods

Ethical statement

Methods in this experiment were performed following the Shahrekord University of Medical Sciences guideline of ethical considerations (Ethics code: IR.SKUMS.AEC.1401.019) and the Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press) of the National Institutes of Health (NIH). All efforts were made to reduce the number of animals and enhance their well-being.

Animals and study plan

Forty-eight male Naval Medical Research Institute (NMRI) mice, weighing 25–30 g, were used. Mice were housed under standard laboratory conditions (12-h dark/light cycle, temperature 23 ± 2 °C, with unrestricted access to water and food) and were randomly divided into six groups ($n = 8$). Group 1, serving as the control group (healthy mice, without induction of colitis), received normal saline at a dose of 1 ml/kg; group 2, the colitis group (colitis induced by acetic acid), received normal saline (1 ml/kg); groups 3–6 were colitis mice treated with UMB (Sigma-Aldrich) (at doses of 12.5, 25, and 50 mg/kg) or dexamethasone (2 mg/kg), respectively. After induction of colitis, drugs were injected via the intraperitoneal (i.p.) route for seven consecutive days. Mice were then subjected to behavioral examinations. After behavioral assessments, mice were euthanized under deep anesthesia using diethyl ether. The hippocampi were quickly removed, placed into liquid nitrogen, and stored at − 70 °C for molecular analyses. Colons were harvested, cut longitudinally, and gently rinsed with a cold saline solution. They were sectioned, fixed in 10% formaldehyde, and embedded in paraffin until further processing for histopathological assessments. The dosage and injection time were selected based on previous evidence and our trial (Shahraki et al. 2020; Karimi et al. 2023). Experimenters were blinded to the experimental groups to minimize potential biases in the experimental procedures and statistical analysis.

Induction of colitis

To induce colitis, after a 24-h fasting period, mice were sedated with an intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). A single dose of 0.2 mL of 7% acetic acid (Merck) was then injected intrarectally, 4 cm proximal to the anus, to induce colitis (Moradipoor et al. 2024).

Forced swimming test (FST)

The forced swimming test (FST) was used to assess depressive-like behaviors in rodents. Animals were placed in a cylinder (80 cm in diameter, 25 cm in height) filled with water. Each animal was observed for immobility when it ceased struggling and floated motionless in the water, making only those movements necessary to keep

its head above water. Behaviors were recorded over 6 min, with immobility duration measured during the final 4 min (Haj-Mirzaian et al. 2019).

Splash test

The splash test assessed self-care activities in rodents. A 10% sucrose solution was sprayed onto the dorsal coat of the animal. Subsequently, grooming behaviors, including cleaning of the nose, face, and head, were recorded for 5 min (Haj-Mirzaian et al. 2019).

Elevated plus maze (EPM)

The EPM is a suitable test for the evaluation of anxiety-like behaviors. The maze was constructed from black opaque Plexiglas and consisted of two closed arms (30 × 5 × 15 cm) and two open arms (30 × 5 cm), connected by a central platform (5 × 5 cm). During the test, each animal was individually placed in the center of the maze, facing one of the closed arms. Mice were allowed to explore the maze for 5 min. The time spent and the number of entries into the open arms were recorded. An arm entry was defined as the placement of all four paws into the arm (Sadeghi et al. 2023). After each test, the maze was cleaned with 70% ethanol to remove any scent cues from previous mice. The test was conducted in a quiet environment with controlled lighting to minimize external disturbances.

Open field test (OFT)

The open field test (OFT) was used to assess locomotion and anxiety-like behaviors in rodents. The OFT apparatus consisted of a Plexiglas box (40 × 50 × 60 cm). Animals were individually placed in the center of the apparatus, and all movements were recorded for 5 min. The time spent in the central area was recorded as a measure of anxiety-like behavior. A decrease in time spent in the central area indicated anxiety-like behavior. The distance traveled (horizontal activity, number of crossings by all four paws over each square) was also recorded. After each trial, the apparatus was cleaned with 70% ethanol (Lorigooini et al. 2020).

Measurement of malondialdehyde (MDA) levels

To measure MDA levels, 100 µL of supernatant from hippocampal samples was mixed with 900 µL of Tris-KCl buffer, followed by the addition of 500 µL of 30% TCA. Subsequently, 500 µL of 0.75% thiobarbituric acid (TBA) was added, and the mixture was heated in a water bath at 80 °C for 45 min. The mixture was then centrifuged (3000 × g for 5 min), and the absorbance of the supernatant was read at 562 nm using an ELISA reader. MDA levels were expressed as nanomoles of MDA per mg of protein (Nagababu et al. 2010).

Measurement of total antioxidant capacity (TAC)

The ferric-reducing ability of plasma (FRAP) assay was used to measure TAC in hippocampal samples. This method measures TAC at 37 °C and pH 3.6. After 30 min, absorbance was measured and reported as the percentage of total ferric-reducing/antioxidant power of antioxidants in protein, with results expressed as micromoles Fe2 + /mg protein (Nasiri-Boroujeni et al. 2021; Benzie and Strain 1999).

Quantitative real-time PCR (qRT-PCR)

The expression of TNF-α, IL-1β, and TLR4 genes was assessed using quantitative real-time PCR (qRT-PCR). Total RNA was isolated from the hippocampus using TRIzol reagent (Invitrogen). qRT-PCR was used to evaluate changes in gene mRNA levels after reverse transcription of 1 µg of RNA from each sample using the PrimeScript RT reagent kit (Takara Bio, Inc., Otsu, Japan). A LightCycler device (Roche Diagnostics, Mannheim, Germany) was used with the SYBR Premix Ex Taq method for qRT-PCR. The B2m gene was used as a housekeeping gene, and the fold change in expression of the target genes was normalized to the housekeeping gene using the $2^{-\Delta\Delta Ct}$ relative expression formula (Omidi-Ardali et al. 2019). The primer sequences for the target genes are listed in Table 1.

Histological evaluations

The colon was sectioned, fixed in 10% formaldehyde, and embedded in paraffin until processing. Five-micron sections were prepared from each sample and stained with

Table 1 Genes and sequences of favorite primers used in PCR amplification

Primer	Forward sequence	Reverse sequence
B2m	GGAAGTTGGGCTTCCCATTCT	CGTGATCTTTCTGGTGCTTGTC
TLR4	ATGGCATGGCTTACACCACC	ATGGCATGGCTTACACCACC
TNF-α	TAGCCATTGTGAAGGAGGGC	CCTGAGGCCGTTCCTTGTAG
IL-1β	GCTCCAGCACTATGTCACCA	CGTCTGAGCTGGAAACCAGT

hematoxylin and eosin (H&E). For scoring, five sections were evaluated from each sample. Histopathological changes in the colon, such as crypt damage, inflammation extent and severity, and percentage of involvement, were scored (Ghasemi-Dehnoo et al. 2022, 2023b). A blinded histopathologist examined the sections.

Statistical analysis

Data analysis was performed using GraphPad Prism version 8. The normal distribution of data was evaluated using the Kolmogorov–Smirnov test, resulting in parametric data. The Brown-Forsythe test was used to assess data homogeneity. Data were presented as mean ± S.E.M and analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Results were considered statistically significant at $P < 0.05$. The α error was set to 0.05, and the power (1-β) was set to 0.8, determining the required sample size as 6–8 mice per group for behavioral assessments and 4–6 samples per group for molecular analyses.

Results

UMB decreased immobility time in FST

As Fig. 1 shows, colitis significantly increased the immobility time in the FST ($P < 0.001$). Moreover, the injection of UMB at a dose of 50 mg/kg to the colitis group significantly reduced the immobility time compared to the saline-treated group ($P < 0.01$). Additionally, the injection of dexamethasone into colitis mice reduced the immobility time compared to the saline-treated group ($P < 0.01$).

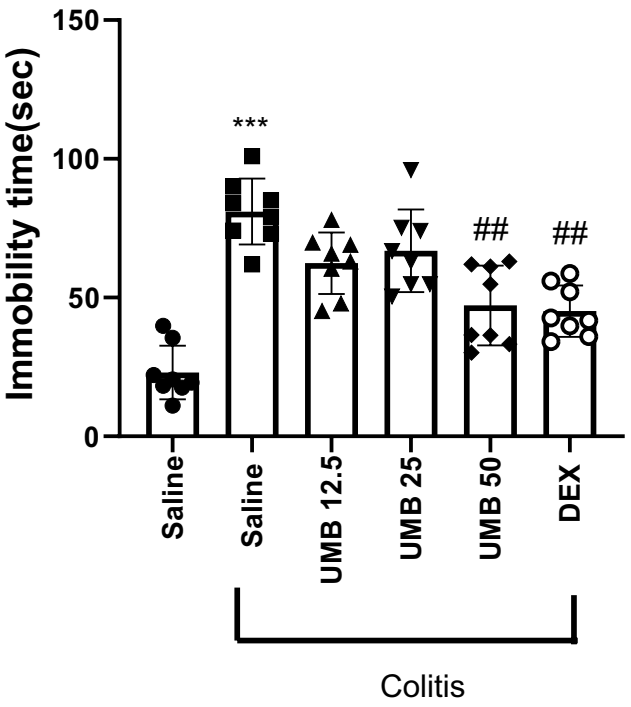


Fig. 1 The effect of UMB on the duration of immobility in the FST. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$ compared to the control group receiving saline; ##$P < 0.01$ compared to the colitis mice receiving saline. UMB, umbelliprenin; DEX, dexamethasone

Effects of UMB on grooming activity time in the splash test

As shown in Fig. 2, colitis significantly decreased the grooming activity time compared to the control group ($P < 0.001$). Furthermore, injecting UMB at 50 mg/kg to the colitis group significantly increased the grooming activity time compared to the saline-treated colitis mice ($P < 0.001$). Administration of dexamethasone to colitis animals also significantly increased grooming activity time compared to the saline-treated colitis mice ($P < 0.01$).

Effects of UMB on horizontal activity in the OFT

The results showed that colitis significantly reduced horizontal activity compared to the control group ($P < 0.001$, Fig. 3). Neither UMB nor dexamethasone had a significant effect on horizontal activity in the OFT.

Effects of UMB on time spent in the central zone in the OFT

The results indicated that the time spent in the central zone of the OFT was significantly reduced in colitis animals compared to the control group ($P < 0.01$, Fig. 4). Treatment of colitis animals with UMB at doses of 25 mg/kg ($P < 0.05$) and 50 mg/kg ($P < 0.01$), as well as dexamethasone ($P < 0.001$), significantly increased the time spent in the central zone compared to the saline-treated colitis mice.

Effects of UMB on open arm entries and time in the EPM

The colitis group showed a significant decrease in open-arm entries compared to the control group ($P < 0.001$) (Fig. 5). Injection of UMB at 50 mg/kg to the colitis group significantly increased open-arm entries compared to the saline-treated colitis mice ($P < 0.001$). Moreover, the time spent in

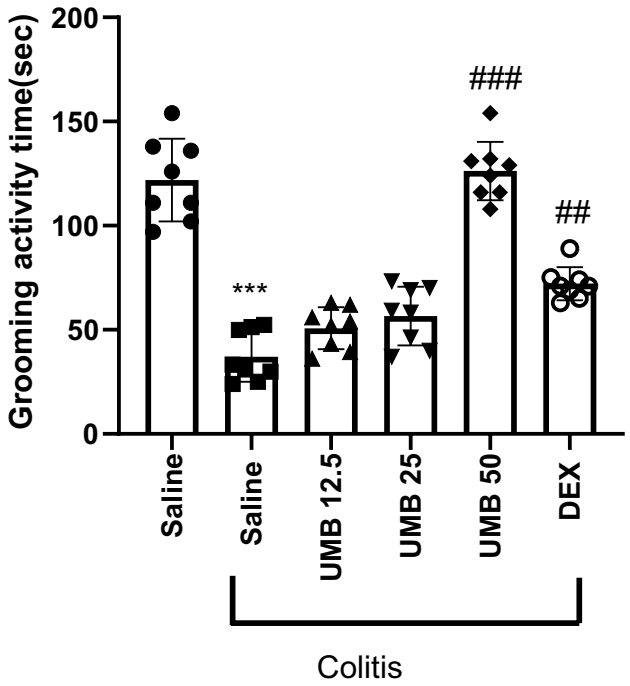


Fig. 2 The effect of UMB on grooming activity time in the splash test. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$ compared to the control mice receiving saline; ##$P < 0.01$ and ###$P < 0.001$ compared to the colitis mice receiving saline. UMB, umbelliprenin; DEX, dexamethasone

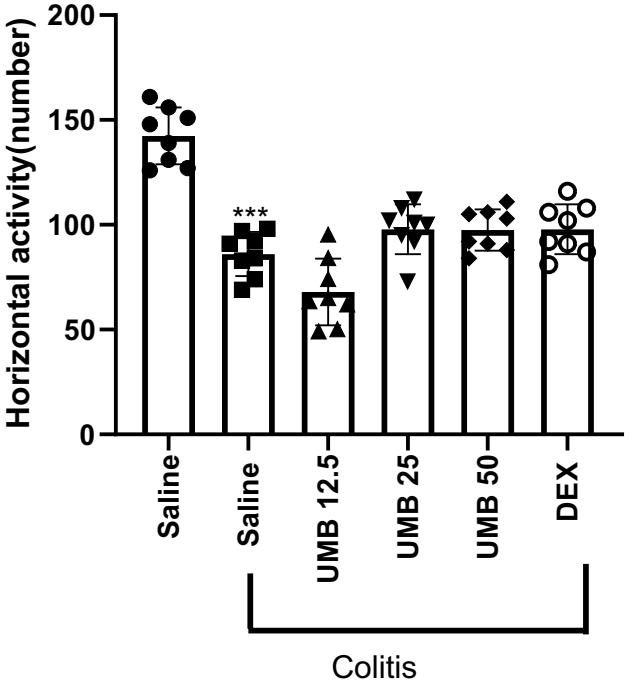


Fig. 3 The effect of UMB on horizontal activity in the OFT. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$ compared to the control group receiving saline. UMB, umbelliprenin; DEX, dexamethasone

the open arms was significantly reduced in the colitis mice compared to the control group ($P < 0.001$). Injection of UMB (50 mg/kg) ($P < 0.001$) and dexamethasone ($P < 0.01$) into colitis mice significantly increased the time spent in the open arms compared to the saline-treated colitis mice.

Effects of UMB on the total antioxidant capacity (TAC) in the hippocampus

As shown in Fig. 6, TAC was significantly reduced in the hippocampus of the colitis group compared to the control group ($P < 0.001$). Injection of UMB at doses of 12.5 mg/kg ($P < 0.05$), 25 mg/kg ($P < 0.001$), and 50 mg/kg ($P < 0.001$), as well as dexamethasone ($P < 0.001$), significantly increased TAC compared to the saline-treated colitis mice.

Effects of UMB on the malondialdehyde (MDA) level in the hippocampus

As shown in Fig. 7, the MDA level was significantly increased in the hippocampus of the colitis group compared to the control group ($P < 0.001$). Administration of UMB at doses of 25 mg/kg ($P < 0.01$) and 50 mg/kg ($P < 0.001$), as well as dexamethasone ($P < 0.05$), significantly reduced MDA levels compared to the saline-treated colitis mice.

Effects of UMB on the expression of inflammatory genes in the hippocampus

Colitis significantly increased the expression of TNF-α ($P < 0.001$), IL-1β ($P < 0.001$), and TLR4 ($P < 0.001$) genes in the hippocampus compared to the control animals (Fig. 8). The results indicated that injection of UMB at doses of 12.5 mg/kg ($P < 0.01$), 25 mg/kg ($P < 0.001$), and 50 mg/kg ($P < 0.001$), as well as dexamethasone ($P < 0.001$), significantly reduced the expression of TNF-α compared to the saline-treated colitis mice. Regarding TLR4, the results showed that injection of UMB at doses of 12.5 mg/kg ($P < 0.001$), 25 mg/kg ($P < 0.001$), and 50 mg/kg ($P < 0.001$), as well as dexamethasone ($P < 0.001$), significantly decreased TLR4 expression compared to the saline-treated colitis animals. The data also showed that injection of UMB at doses of 12.5 mg/kg ($P < 0.001$) and 25 mg/kg ($P < 0.001$), as well as dexamethasone ($P < 0.001$), significantly reduced IL-1β expression compared to the colitis animals receiving saline.

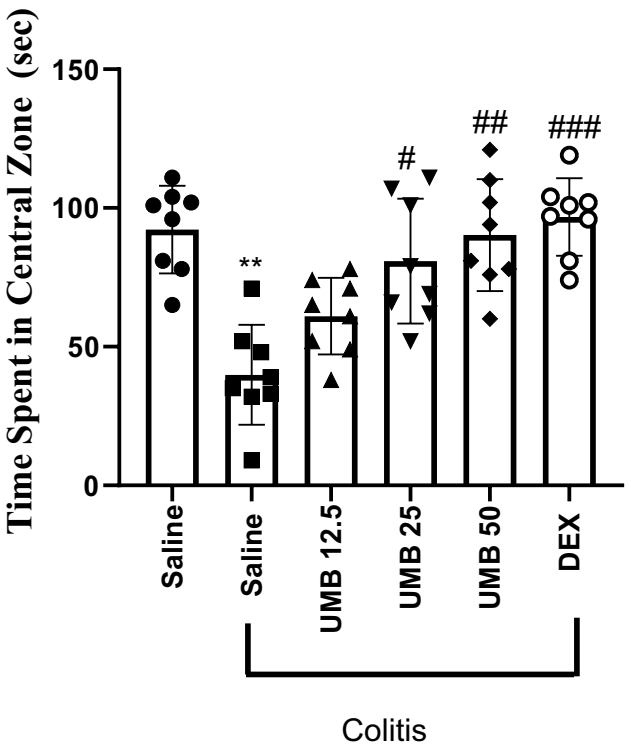


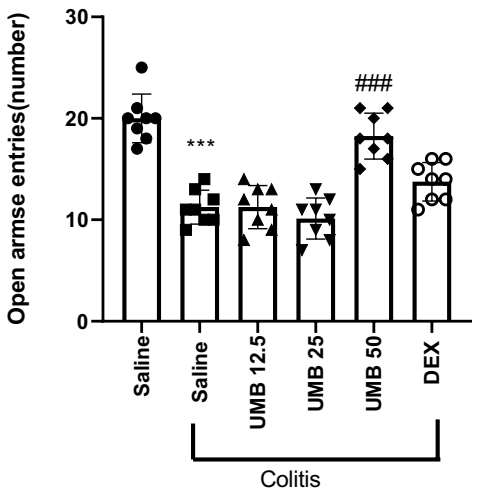
Fig. 4 The effect of UMB on time spent in the central zone in the OFT. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. $^{**}P < 0.01$ compared to the control mice receiving saline; $\#P < 0.05$, $\#\#P < 0.01$, and $\#\#\#P < 0.001$ compared to the colitis mice receiving saline. UMB, umbelliprenin; DEX, dexamethasone

Effect of UMB on the histopathological deviations in the colon

Representative images of histopathological modifications in the colon tissue are shown in Fig. 9. As demonstrated, the colon tissue in the control group exhibited a normal microscopic appearance. However, in the colitis group, indications of epithelial injury, increased epithelial thickness, edema, and infiltration of inflammatory cells in the colon were observed. Treatment with UMB and dexamethasone reduced epithelial damage, epithelial thickness, edema, and inflammatory cell infiltration in the colon.

Discussion

The current study aimed to assess the effects of UMB on comorbid behavioral disorders in experimental colitis in mice, focusing on oxidative stress and the neuro-immune response in the hippocampus. The findings of this study revealed that induction of colitis with acetic acid led to histopathological alterations, including mucosal, submucosal, and crypt-related damages, along with the infiltration of inflammatory cells in the colon. We observed that colitis was associated with an increase in immobility time in the FST, a reduction in the entries and time spent in the open arms of the EPM, a decrease in grooming activity in the splash test, and a reduction in the time spent in the central zone of



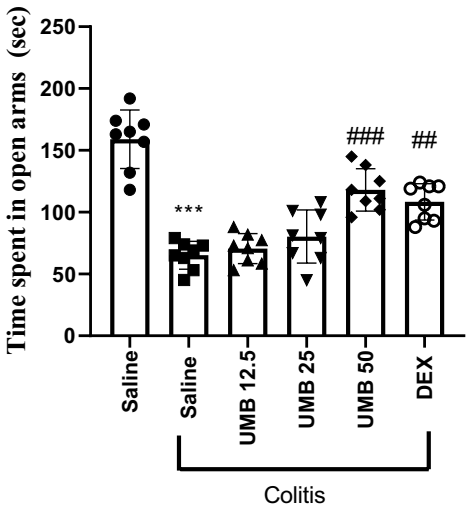


Fig. 5 The effect of UMB on open-arm entries and time spent in open arms in the EPM. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. $^{***}P < 0.001$ compared to the control mice receiving saline; $\#\#P < 0.01$ and $\#\#\#P < 0.001$ compared to the colitis mice receiving saline. UMB, umbelliprenin; DEX, dexamethasone

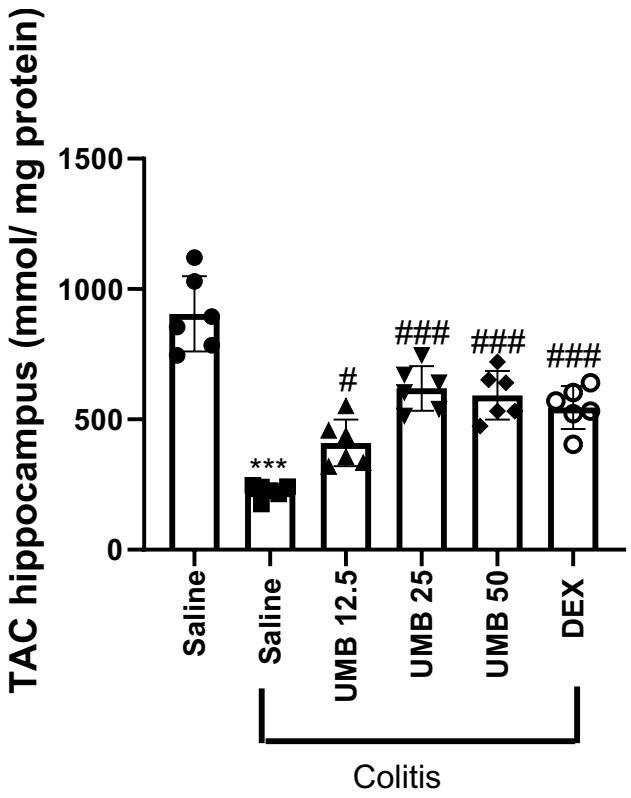


Fig. 6 The effect of UMB on the total antioxidant capacity (TAC) in the hippocampus. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$ compared to the control animals receiving saline; #$P < 0.05$, ##$P < 0.01$, and ###$P < 0.001$ compared to the colitis mice receiving saline. UMB, umbelliprenin; DEX, dexamethasone

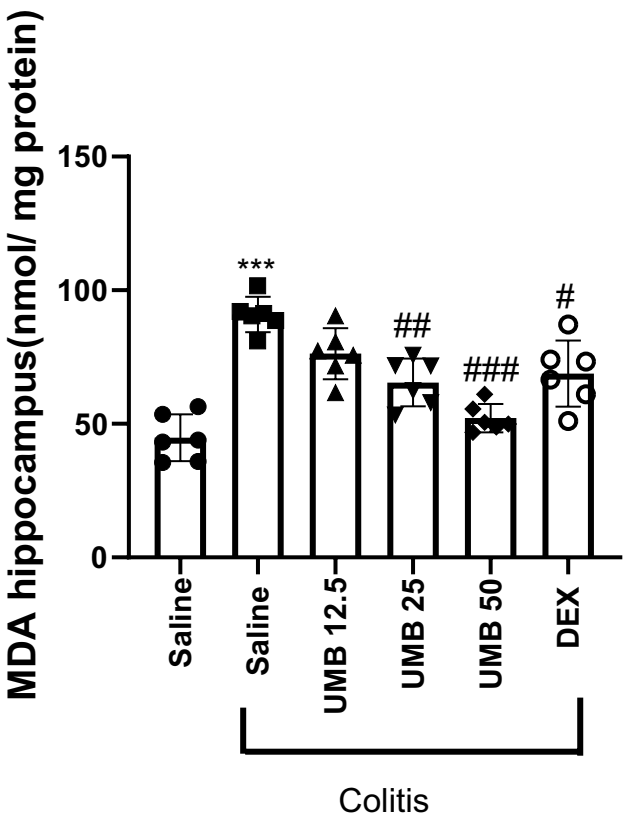


Fig. 7 The effect of UMB on the malondialdehyde (MDA) level in the hippocampus. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$ compared to the control animals receiving saline; #$P < 0.05$, ##$P < 0.01$, and ###$P < 0.001$ compared to the colitis mice receiving saline. UMB, umbelliprenin; DEX, dexamethasone

the OFT. These results suggest that experimental colitis is linked to depressive- and anxiogenic-like behaviors in mice. Additionally, colitis was associated with decreased TAC and increased MDA levels, along with elevated expression of inflammatory markers in the hippocampus. Investigating the potential effects of UMB, we found that UMB alleviated comorbid behavioral disorders of colitis and attenuated neuroinflammation and oxidative stress in the hippocampus following colitis. UMB also mitigated histopathological alterations in the colon.

Extraintestinal manifestations often accompany IBD. These include conditions affecting the skin (e.g., pyoderma gangrenosum, erythema nodosum), joints (e.g., peripheral arthritis), eyes (e.g., uveitis, mild conjunctivitis), hepatobiliary tract (e.g., primary sclerosing cholangitis), lungs, heart, vascular system, kidneys (e.g., IgA nephropathy, minimal change glomerulonephritis, membranoproliferative glomerulonephritis), and the central and peripheral nervous systems (e.g., demyelinating diseases such as multiple sclerosis and ischemic optic neuropathy) (Ott and Scholmerich 2013; Zois et al. 2010). In recent years, there has been increasing interest in uncovering the physiological pathways that connect the gut and brain (Omidi-Ardali et al. 2019). It has been established that alterations in gut function are linked to psychiatric and behavioral conditions, such as anxiety and depression (Neufeld et al. 2023; Tan 2023). This relationship supports the hypothesis that gastrointestinal system homeostasis plays a crucial role in brain function and development (Hu et al. 2016; Fiorentino et al. 2016; Bisgaard et al. 2022). Studies have shown a connection between inflammatory bowel disease (IBD) and behavioral disorders, indicating that both acute and chronic colitis are associated with behavioral disorders (Bernstein et al. 2019; Haj-Mirzaian et al. 2017; Matisz et al. 2020; Noubissi et al. 2022). From a biological standpoint, the mechanisms underlying this link are complex and not fully understood. Haj-Mirzaian et al. demonstrated that the induction of acute colitis in rats provoked behavioral disorders, with abnormal mitochondrial function and neuroinflammation in the hippocampus implicated in the comorbidity of anxiety and depression in the early stages of Crohn's disease (Haj-Mirzaian et al. 2017). One central theory highlights the role of the Brain-Gut Axis in establishing and maintaining this relationship (Qian et al. 2022;

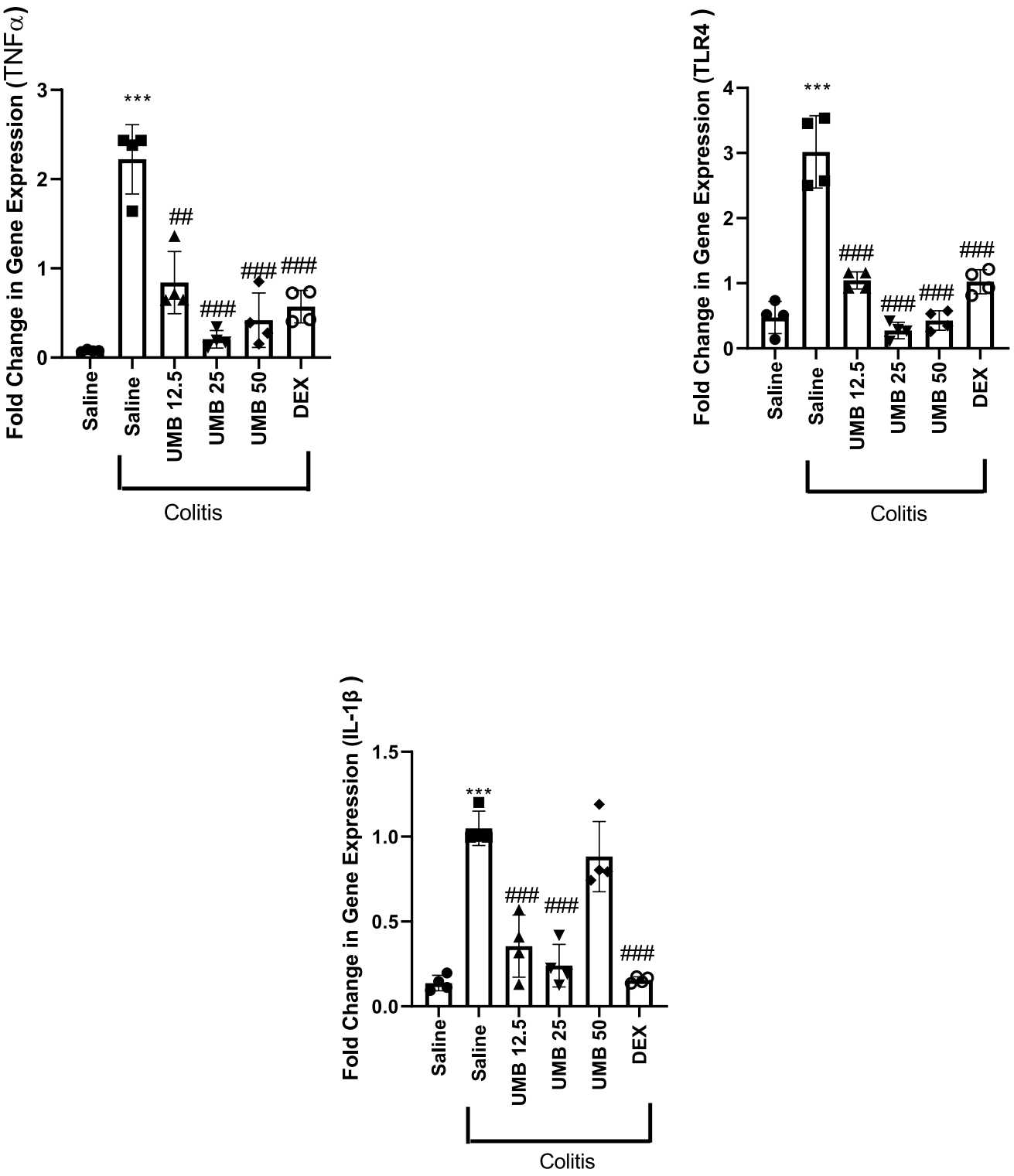


Fig. 8 The effect of UMB on the expression of TNF-α, IL-1β, and TLR4 in the hippocampus. Data are presented as mean ± S.E.M ($n = 8$) and analyzed by one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$ compared to the control animals receiving saline; ##$P < 0.01$ and ###$P < 0.001$ compared to the colitis animals receiving saline. UMB, umbelliprenin; DEX, dexamethasone

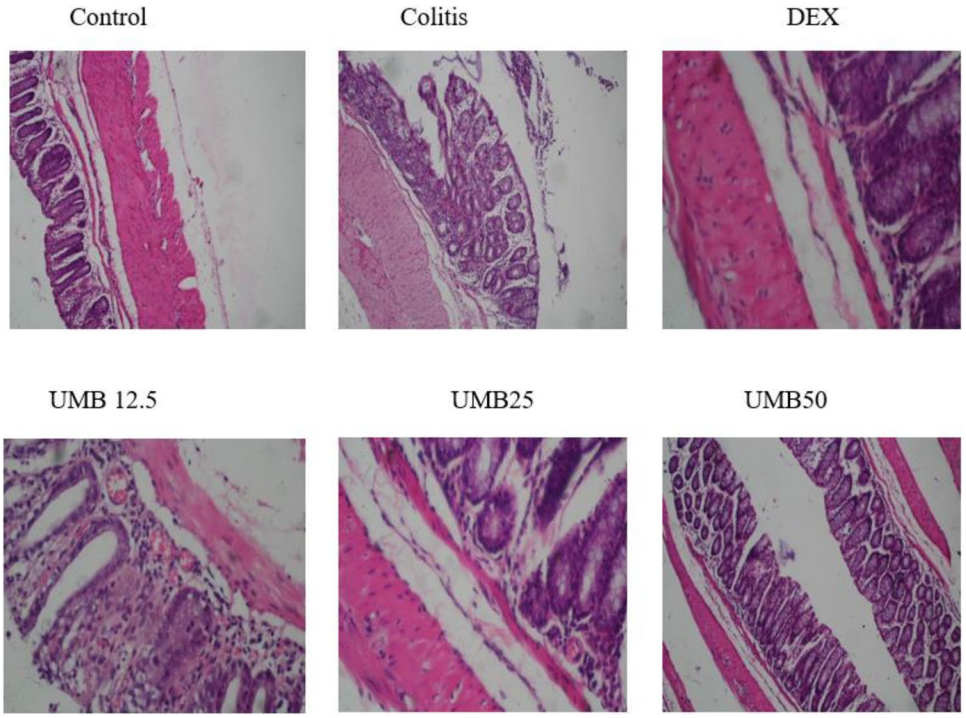


Fig. 9 Representative Hematoxylin and Eosin staining of colonic sections. Compared with the control group, epithelial damage, increased epithelial thickness, edema, and inflammatory cell infiltration are seen in the colitis group. Treatment with UMB and dexamethasone decreased the aforementioned alterations in the colon

Uellendahl-Werth et al. 2022). Neurological complications in IBD range from 0.25% to 47.5% (Diesing 2023). Several factors contribute to neurological disorders associated with IBD, including nutrient deficiencies due to malabsorption and complications arising from medical and surgical management (Singh et al. 2012). Surprisingly, previous studies have shown that neurological manifestations can precede gastrointestinal symptoms of IBD (Gluch et al. 2022). This suggests that the gut and brain communicate bilaterally, and disturbances in the function and regulation of one can impact the other (Bonaz et al. 2018; Sandhu et al. 2017; Bosi et al. 2020; Misiak et al. 2020). However, the exact mechanisms involved in the comorbidity of anxiety and depression in IBD remain unclear. The findings of the current study confirmed that experimental colitis is associated with depressive- and anxiogenic-like behaviors in male mice, evidenced by decreased time spent and entries into the open arms in the EPM, reduced grooming activity in the splash test, decreased time spent in the central zone of the OFT, and increased immobility time in the FST.

Ample evidence suggests the involvement of neuroinflammation and oxidative stress in the pathophysiology of psychiatric disorders (Li et al. 2019; Nakao et al. 2021). TLR4 initiates a series of signaling cascades that result in the activation of nuclear factor kappa B (NF-κB). Upon activation of this signaling pathway, an inflammatory process is triggered, leading to the production of inflammatory cytokines such as TNFα and IL1β. As previous studies have shown, neuroinflammation through the TLR4/NF-κB pathway is involved in cognitive and behavioral problems (Soltani et al. 2022; Zheng et al. 2012). Previous evidence has demonstrated that sterile inflammation in the hippocampus is associated with behavioral issues such as depression and anxiety, highlighting the hippocampus's essential role in mediating behavior (Mozafari et al. 2020; Famitafreshi and Karimian 2020). Elevated levels of inflammatory cytokines in the serum of depressed patients have been directly linked to suicidal ideation (O'Donovan et al. 2013). Agents with anti-inflammatory properties could alleviate symptoms of anxiety and depression and potentiate the efficacy of related drugs (Jia et al. 2017; Uher et al. 2012; Habtemariam 2019). The results of the current study showed that comorbid behavioral disorders in colitis mice are associated with an increase in oxidative stress in the hippocampus, as indicated by decreased TAC and increased MDA levels. Additionally, we found that behavioral disorders following colitis are associated with increased expression of genes related to neuroinflammation, including TNFα, IL1β, and TLR4 in the hippocampus. Our results suggest that the activation of oxidative stress and inflammation in the hippocampus contributes, at least in part, to comorbid depressive- and anxiogenic-like behaviors following colitis.

Several studies have shown that acetic acid-induced colitis in mice is associated with epithelial damage, edema, and infiltration of inflammatory cells into the epithelium of the colon (Ghasemi-Dehnoo et al. 2023a, 2023b). In the current study, we observed infiltration of inflammatory cells and edema, along with epithelial lesions, in the colon tissue.

UMB, a member of the coumarin family, has been demonstrated to possess neuroprotective properties (Fiorito

et al. 2022). Due to the lipophilic nature and low polarity of sesquiterpenes like UMB, they can cross the blood–brain barrier (BBB) and enter the brain. The presence of a hydrophobic chain at the C7OH position of the 1,2-benzopyrone ring enhances the lipophilic properties of UMB, facilitating cell membrane infiltration (Shahzadi et al. 2020; Arya et al. 2021; Karimi et al. 2023). Recent studies have described its immunomodulatory, anticancer, neuroprotective, and analgesic characteristics (Hashemzaei et al. 2015; Rashidi et al. 2018). Numerous studies have confirmed its antioxidative and anti-inflammatory effects (Shakeri et al. 2014; Karimi et al. 2023). Moreover, UMB has demonstrated anti-inflammatory properties through the modulation of cytokine secretion (Khaghanzadeh et al. 2017). The results of the present study indicate that the injection of UMB into colitis animals mitigated depressive- and anxiogenic-like behaviors, as evidenced by increased grooming activity in the splash test, increased time spent and entries into the open arm in the EPM test, decreased immobility time in the FST, and increased time spent in the central zone of the OFT. Consistent with previous studies, these findings suggest antidepressant- and anxiolytic-like effects in rodents (Haj-Mirzaian et al. 2017). These behavioral findings indicate that UMB partially reduced depressive- and anxiogenic-like behaviors following the induction of colitis in mice. Furthermore, we found that treatment of colitis mice with UMB decreased MDA levels and increased TAC in the hippocampus, indicating its antioxidative effects. In terms of neuroinflammation, our results show that UMB decreased the expression of TNFα, IL1β, and TLR4 in the hippocampus of colitis mice, indicating its anti-neuroinflammatory effect. Additionally, the findings showed that UMB reduced edema, epithelial damage, and infiltration of inflammatory cells in the colon tissue. However, further studies are needed to fully understand the exact mechanisms underlying comorbid behavioral disorders in colitis and the effects of UMB in alleviating these behaviors. One limitation of our study is that we only assessed TNFα, IL1β, and TLR4 at the gene level. Future studies should evaluate these markers at the protein level using techniques such as western blotting, ELISA, or IHC. Another limitation is that we did not investigate the effects of UMB on comorbid behavioral disorders in colitis following the induction of colitis in female mice.

Conclusion

In conclusion, our findings suggest that the activation of oxidative stress and neuroinflammation in the hippocampus contributes, at least partially, to the development of depressive- and anxiogenic-like behaviors observed following the induction of colitis in mice. The results indicate that UMB may partially alleviate comorbid behavioral disorders following experimental colitis in male mice by reducing oxidative stress and the neuro-immune response in the hippocampus.

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Authors contribution N.H: Completed the experimentations; wrote the manuscript. Z.L: Completed the experimentations; wrote the manuscript. R.M: Analyzed and interpreted the data wrote the manuscript. H A-K: Conceived and planned the experimentations; contributed reagents, materials, analysis tools, or data; completed the experimentations; wrote the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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Data availability Data is provided within the manuscript.

Declarations

Ethical approval Methods in this experiment were performed following the Shahrekord University of Medical Sciences guideline of ethical considerations (Ethics code: IR.SKUMS.AEC.1401.019) and the Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press) of the National Institutes of Health (NIH). All efforts were made to reduce the number of animals and enhance their well-being.

Consent to participate Not applicable.

Consent for publication All authors reviewed and approved the manuscript.

Competing interests The authors declare no competing interests.

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