NF-KB AND NRF2 PATHWAYS CONTRIBUTE IN THE DEVELOPMENT OF ACUTE AND CHRONIC ULCERATIVE COLITIS INDUCED IN MICE BY DEXTRAN SULPHATE SODIUM

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ABSTRACT

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) and it is characterized by high recurrence and relapsing risk. UC affects millions of people worldwide but its pathophysiology remains unclear. In this study, the UC models of BABL/c mice were induced by dextran sulfate sodium (DSS) [3.5% (w/v) for 7 days (acute UC) or 1.5% (w/v) for 2 weeks (chronic UC)]. Herein, we aimed to determine the expression levels of nuclear factor κB (NF-κB), interleukin-1β (IL-1β), nuclear factor erythroid 2–related factor 2 (Nrf2), Superoxide dismutase (SOD) and nitric oxide (NO) production during acute and chronic DSS-induced colitis in mice and to assess their possible role in the pathogenesis of the disease. Our results showed an increased level of NF-κB, IL-1β and NO in ulcerative colitis group while the levels of both Nrf2 and SOD were markedly decreased. Also, we found a significantly increased levels of NF-κB during the acute and chronic experimental colitis, (P < 0.05 and P <0.01 respectively) compared to control. Moreover, the level of pro-inflammatory cytokine IL-1β was increased in response to the elevated level of NF-κB in both the acute and chronic UC (P < 0.01). Interestingly, we found a significant variation in the expression levels of IL-1β between the acute and chronic DSS-induced colitis (P < 0.01) that seems to be essential for the development of the UC from the acute to the chronic phase. These findings suggested that changing in NF-κB and Nrf2 pathways may be contributed in the development of both the acute and chronic DSS-induced UC in mice. Also, both of NF-κB and IL-1β enhance the development of UC and the progression of the acute intestinal inflammation into the chronic phase. Additionally, IL-1β could be used as diagnostic biomarkers to differentiate between the acute and chronic UC.

Keywords: Dextran sodium sulfate; Ulcerative colitis; NF-κB; Nrf2; IL-1β; NO; SOD
INTRODUCTION

Ulcerative colitis (UC) and Crohn’s disease (CD) are the two major forms of inflammatory bowel disease (IBD) (Kaser et al., 2010). UC is a kind of chronic intestinal inflammation mediated by an immune system disorder (Ungaro et al., 2017). As an autoimmune disease, UC has become known as a universal health problem and has been documented by the World Health Organization (WHO) as a refractory disease (da Silva et al., 2014). The main pathological features of UC include local ulcers and chronic inflammation of the colon, difficult to cure, and it is likely to recurrent attacks (Lin et al., 2019).

Epidemiological studies of IBD have showed that over 2 million individuals in the North America, 3.2 million in Europe, and millions more worldwide have been diagnosed with IBD (Ananthakrishnan et al., 2020). The incidence of UC has been high, not only in Western countries, but also has been increasing year by year in developing countries with an annual growth rate of 14.9% (Ng et al., 2018). In Egypt, a study investigating IBD incidence from 1995 to 2009 showed a constant rise in the incidence of IBD, specially UC (Esmat et al., 2014).

One of the most common IBD-related models is the dextran sulfate sodium (DSS)-induced colitis. The administration of DSS polymers in drinking water induces colitis and is useful for studying the involvement of innate immune mechanisms. Indeed, the great majority of published papers have used animal models in acute periods, but as well-known UC is chronic a disease. Therefore an important feature of this model is that the administration of DSS at high dose for a short period leads to acute colitis while the administration of low dose DSS for a long period leads to chronic intestinal inflammation, which permits important observations about the adaptive immune system (Okayasu et al., 1990; Tanaka et al., 2003) and allows studies of mediators involved in the chronic process of IBD.

The pathogenesis of UC is not yet clear and may involve genetic, environmental, immune, infectious and other factors (Scarpa et al., 2014). Despite this, activation of the nuclear transcription factor kappa B (NF-κB ) signaling pathway and the initiation of related inflammatory factors such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) play critical roles in promoting the development of inflammatory disease (Yadav et al., 2016).

NF-κB has the ability to promote the expression of various pro-inflammatory cytokines like interleukine-6 (IL-6) and interleukine-1β (IL-1β) (Atreya et al., 2008). IL-1β acts as an amplifier of immune reactions and it can modulate the function of both immune and non-immune cells through its action on IL-1 receptors (IL-1R) (Coccia et al., 2012; Dinarello, 2014). Also, it promotes the activation of dendritic cells, macrophages, and neutrophils and the expressions of other inflammatory cytokines facilitating the neutrophil infiltration (Wu et al., 2015).

Amongst the immune-regulatory factors, oxidative stress is one of the major contributing factors involved in the development of the chronic disease and may be secondary to inflammation (Hamouda et al., 2011). Nitric oxide (NO) is a lipophilic-
free radical, which plays a key role in regulating homeostasis of many biological systems (Avdagic et al., 2013). Elevated levels of NO may be toxic and may damage healthy tissue (Kolios et al., 2004; Palatka et al., 2005; Avdagic et al., 2013).

The nuclear factor erythroid 2–related factor 2 (Nrf2) is a key transcription factor which regulates the expression of cytoprotective genes in response to oxidative stress (Bai et al., 2016). Under conditions of homeostatic cell growth, the cytoplasmic protein Keap 1 interacts with Nrf2, and represses its function. However, under oxidative stress conditions, Nrf2 is released from Keap 1 and translocate into the nucleus, then binds to antioxidant responsive element (ARE), resulting in the activation of various antioxidant enzymes, such as Superoxide dismutase (SOD) (Harder et al., 2015).

Moreover, Superoxide dismutase (SOD) has been demonstrated to play a critical role in the redox modulation in acute disease; where it convert the superoxide anion ($O_2^•$), into the easily diffusible and stable metabolite hydrogen peroxide ($H_2O_2$) and then catalase acts on $H_2O_2$ and neutralizes it into $H_2O$ (Pravda, 2005; Karp and Koch, 2006).

The aim of the present study was to evaluate the alterations in the levels of NF-κB, IL-1β, NRF2, NO and SOD during acute and chronic DSS-induced colitis in mice and to study their possible role in the progression of the disease.

MATERIALS AND METHODS

Chemicals and reagents

Dextran sulfate sodium (DSS, CAS no. 9011-18-1, molecular weight of approximately 40,000 Daltons) was provided by Bio-diagnostics Company (Giza, Egypt). NF-κB p65, IL-1β, Nrf2 and β-actin were supplied by Santa Cruz Biotechnology, (Texas, USA), BCIP/NBT substrate detection Kit (South San Francisco, USA). All other reagents used were of analytical grade.

Animals

Twenty-four 8-10-week-old specific pathogen-free male BALB/c mice, weighing approximately 12 g, were obtained from the animal house (Assiut University, Egypt). The mice were allowed to acclimatize for 2 weeks. Rats were housed (2 per cage) in a regulated environment (temperature, 20-22°C; humidity, 50 ±5%; night/day cycle, 12 hours) with free access to standard diet pellets and sterile tap water ad libitum. Handling and experimentation were performed in accordance with The International Ethical Guidelines concerning the care and use of laboratory animals and the experimental protocol was approved by the Scientific Research Ethics committee of Faculty of Pharmacy, Assiut University.

Experimental design and induction of colitis by DSS in mice

After 2 weeks of acclimatization, the animals were randomly divided into three groups 8 for each, the first one served as the control and given autoclaved tap drinking
water. In group 2 acute colitis was induced by administering 3% (w/v) DSS in the drinking water for 7 days. The last group was fed with 1.5% DSS for 14 days to induce chronic UC (Nishihara et al., 2006; Perse and Cerar, 2012; Chassaing et al., 2014). Mice were weighed every day, body weights of mice in the three groups were determined and recorded every day, and body weight change was calculated as a percentage of the initial weight on day 1 as follows:

\[
\text{Body weight change on day } x \text{ (\%)} = \frac{\text{body weight of day } x}{\text{body weight of day 1}} \times 100
\]

Assessment of colon damage by histopathology study

Animals were sacrificed 24 h fasting after the last day of the study (7th day for acute and 15th for chronic), after termination, colon tissue samples were isolated from the mice, fixed in neutral buffered formalin 10% and processed by paraffin embedding technique. Transverse sections of 4-5 μm thick were prepared and stained with Haematoxylin and Eosin (Bancroft and Gamble, 2008) for light microscopic examination. A semi-quantitative histological assessment of colon lesions was carried out, three sections of hematoxylin/ eosin-stained colon were examined using a light microscope (Olympus BX45). The severity of histopathological alterations was blindly scored by an experienced pathologist.

Western Blotting Assessments of NF-κB p65, IL-1β and Nrf2 Proteins

Proteins were harvested from colon tissue samples with Lysis Buffer supplemented with protease inhibitor and phosphatase inhibitor. Total protein content in the supernatant was determined by using biuret reaction method (Gornall et al., 1949). The denatured protein samples were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Fifty microgram proteins were separated by 12% glycine sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride (PVDF) membranes. Membranes were blocked with 5% Defatted milk in tris-buffered saline containing 0.1% Tween 20 (TBST) for 1 hour at room temperature and incubated overnight at 4°C with primary antibodies targeting NF-κB p65 (1: 5000; Santa Cruz Biotechnology, Inc), IL-1β (1: 5000; Santa Cruz Biotechnology, Inc) and Nrf2 (1: 5000; Santa Cruz Biotechnology, Inc). The blots were then incubated with secondary antibodies for 1 hour at room temperature and the membrane bound antibodies were detected with a commercially available BCIP/NBT substrate detection Kit (Genemed Biotechnologies, Inc, USA). Normalization was performed by β-actin (1:5000; Santa Cruz Biotechnology, Inc). Each analysis was repeated to assure reproducibility of results. Quantification of each corresponding analysis was further performed using Image J software and expressed as the relative band density to the β-actin.

Determination of nitric oxide and superoxide dismutase in colon tissue

The NO concentration in colon tissues was determined by measuring nitrite concentration, a stable metabolic product of NO with oxygen. The nitrite concentration was determined by classic colorimetrical Griess reaction, stander curve of sodium nitrite
was constructed to calculate the concentration of NO in our samples (Montgomery and Dymock, 1961; Ibragic et al., 2012).

Estimation of SOD activity in the colon tissues was carried out by a kinetic procedure that based on the ability of SOD to inhibit the auto-oxidation of pyrogallol (Marklund, 1985). The enzymatic activity is directly proportional to the activity of SOD in the tested sample and was expressed as U/mg protein.

Statistical analysis:

Data were expressed as the mean ± standard deviation (SD). The statistical differences between groups were determined by means of one-way ANOVA followed by Tukey’s multiple comparison test. Statistical analyses were performed with Graph Pad Prism 8 software (Graph Pad Software Inc., San Diego, CA). A P value of less than 0.05 (P < 0.05) was considered to be statistically significant.

RESULTS

Ulcerative colitis-induced body weight loss

Body weights of mice in the three groups were determined and recorded every day, and body weight change was calculated as described in the material and methods. Our results demonstrated that induction of UC by DSS caused marked stepwise body weight decrease. Several factors may have contributed to this weight loss; mice bled through their anus and suffered from bloody diarrhea. In addition, their daily food intake was lower than that of the healthy mice in the control group. In contrast, mice in the control group gained weight throughout the study period (Fig. 1A) (Fig. 1B). Mice with DSS-induced colitis showed massive body weight loss, diarrhea, and gross anal bleeding with an increased disease activity index (DAI) score that peaked at day 7 in the acute colitis group (Fig. 1C) and day 15 in the chronic group (Fig. 1D).

Figure 1: Weight change and disease activity index during the progression of DSS-induced colitis: Data are reported as means ± S.D. of six mice per group.
Table 1: Disease activity index (DAI) scoring system

| DAI scores | Weight loss (%) | Stool consistency | Occult/gross bleeding |
|------------|-----------------|-------------------|-----------------------|
| 0          | 0               | Normal            | None                  |
| 1          | 1–5             | Normal            | None                  |
| 2          | 6–10            | Loose stools      | Slightly bleeding     |
| 3          | 11–20           | Loose stools      | Slightly bleeding     |
| 4          | >20             | Diarrhea          | Gross bleeding        |

DAI scores were determined by combining scores of body weight loss, stool consistency and Gross bleeding.

Macroscopic changes and Histopathological findings in the three experimental groups:

The length of colon is a classical marker of intestinal pathology in colitis. The DSS groups had remarkably shorter colons than the normal control (Fig. 2), suggesting a marked intestinal pathological condition induced by drinking of DSS. Histopathological investigation revealed that colon tissue specimens from the control group demonstrate normal histological and glandular structures of the mucosa, submucosa, and muscularis. In contrast, colon tissue specimens from the disease groups showed focal ulceration in the mucosal lining epithelium with underlying necrosis and inflammatory cell infiltration in the lamina propria, as well as crypt damage.

Figure 2: Representative Macroscopic changes and Histopathological findings in: (A) Colon of normal control mice showing the normal histological architecture (mucosa, Crypts of Lieberkühn, submucosa and muscularis layers) (H & E, scale bar 100um). (B) Colon of mice treated with DSS (3%) for 7 days showing focal mucosal necrosis (short arrow), submucosal edema (long arrow) and inflammatory cells infiltration (arrow head) (H & E, scale bar 100um). (C) Colon of mice treated with DSS (1.5%) for 2 weeks showing marked mucosal necrosis, crypt abscesses and ulcers (arrow) (H & E, scale bar 100um).
Effect of UC induction on tissue expression of NF-κB, IL-1β and Nrf2

Western blot was used for evaluation of NF-κB, IL-1β, and Nrf2. The results of this study showed that NF-κB was increased significantly in both acute and chronic DSS induced UC (P < 0.05; P < 0.01 respectively) compared with the control group (Fig. 3A). Similarly, western blot analysis revealed that IL-1β expression was significantly increased (P < 0.01) in the two groups of disease induced by DSS (Fig. 3B).

Also, we examined the protein expression of Nrf2 in colonic tissue during the exposure of mice to DSS. The western blot analysis showed a significant decrease in Nrf2 protein expression in the ulcerative groups (P < 0.01) (Fig. 3C).

Figure 3: The Expression patterns of NF-κB, IL-1β and Nrf2 protein levels in colon tissue of DSS treated and untreated mice (n = 7 samples per group): (A) Expression of NF-κB tissues were normalized to β-actin. (B) Expression of IL-1β in colon tissues were normalized to β-actin. (C) Expression of Nrf2 in colon tissues were normalized to β-actin. Data are reported as means ± S.D. of six mice per group *P < 0.05; **P < 0.01 compared with the control group and #P < 0.05 compared with the acute UC group. The data come from three independent experiments.
Colon tissue concentration of nitric oxide and Superoxide dismutase

Compared to the Control group, the Mean of the colon tissue NO significantly increased in both groups of DSS-induced colitis ($P < 0.05$) for acute UC and ($P < 0.001$) chronic UC (Fig. 4A). On the contrary, the concentration of SOD in the acute and chronic UC significantly decreased ($P < 0.01$ and $P < 0.001$ respectively) (Fig. 4B).

**Figure 4:** The Nitric oxide and Superoxide dismutase level in colon tissues of mice treated with DSS and control. Data are reported as means ± S.D. of six mice per group

* $P < 0.05$; **$P < 0.01$ and ***$P < 0.001$ compared with the control group.

**DISCUSSION**

IBD is an autoimmune disease affecting the gastrointestinal tract characterized by chronic relapsing remitting inflammation, which is accompanied by bleeding in the stools, and can eventually progress to colorectal carcinoma (CRC). The current study showed a stepwise decrease in the body weight of DSS-treated colitis mice along the progression of disease since day 4 in acute group and day 6 in the chronic colitis and did not recover at the end of the experiment. Whereas, the normal healthy control group exhibited profound body weight gain at the end of the experiment (Fig. 1). The severity of manifestations was progressively intensified towards the termination of experiment, where mice exhibited watery feces and gross bleeding on the anus site (Fig. 1).

Several factors may responsible for this observation including bloody diarrhea and the loss of appetite and consequently negative effect on the food intake where the daily food intake in UC groups was noticeably deceased comparing to the normal control group. Other causes of weight loss include, the inflammatory state in UC which results in mal-absorption of nutrients; a generalized catabolic state; and alterations in the levels of metabolic hormones (Hwang et al., 2012). These results was in agreement with some of the previous studies. Tsai et al. showed that treatment of C57BL/6 mice with 3% DSS for 5 days, resulted in significant weight loss compared to control mice who did not receive DSS at all (Tsai et al., 2016). Additionally, Zhou, Tan et al. reported that induction of acute ulcerative colitis by adding of DSS to the drinking water to a final concentration of 3% (weight/volume) for seven consecutive days also lead to significant decrease in the body weight of mice (Zhou et al., 2017).

DAI scores have been reported to be a main parameter in the evaluation of severity of UC (Zhang et al., 2019). In the current study, DSS administration
significantly increased the of DAI scores (**Fig. 1C and 1D**) indicating a clinical inflammation-exacerbation effect of DSS in the disease groups.

In the present study, we found that induction of UC in mice treated with DSS (3%) for 7 days (**Fig. 2B**) resulted in focal mucosal necrosis, sub-mucosal edema and inflammatory cells infiltration, while in case of mice treated with DSS (1.5%) for 2 weeks (**Fig. 2C**), they showed marked mucosal necrosis, sub-mucosal edema crypt abscesses and ulcers and inflammatory cells infiltration compared to the normal control group. These results were in accordance with Chassaing, Aitken et al. who reported that UC is usually associated with abnormalities in the histological structure of the intestine like ulcerations, loss of crypt architecture, and inflammatory cell infiltration (**Geboes, 2003**).

Over the past 20 years much research has highlighted the importance of understanding the pathogenesis of IBD for the development of efficient and safe pharmacological treatments. In this context, we investigated some of the immunological events that occur during acute and chronic phases. Previous studies reported that NF-κB signaling pathway plays an important role in the process of inflammation; owing to its effects on the regulation and maintenance of homeostasis of pro-inflammatory cytokines as IL-1β and TNF-α (**Niu et al., 2015; Liu et al., 2017**). In the present study we examined the NF-κB signaling pathway protein in mouse colon tissue. Our results showed that compared with normal control group, the expression level of NF-κB p65 was significantly increased in both the acute and chronic phases of UC groups when compared with control (P > 0.05 and P > 0.01; respectively) (**Fig. 3A**). These results demonstrating that the NF-κB signaling pathway in model group mice was significantly activated and related with the severity of UC. Similar studies were reported that the NF-κB signaling pathway was abnormally activated in both IBD patients and DSS-induced acute UC mouse models (**Atreya et al., 2008; Liu et al., 2018**).

To investigate the downstream effect of NF-κB we estimated the expression of IL-1β since its synthesis and release are tightly regulated by NF-κB pathway (**Dinarello, 1996**). Our results showed that the colonic tissue expression level of IL-1β was significantly increased in the ulcerative groups (Figure 3B) and it was related to the degree of disease progression where the maximum expression level of IL-1β was seen in the chronic UC group. This result was consistent with the results reported by Coccia, Harrison et al. 2012 who reported that the chronic intestinal inflammation correlates with increased local secretion of IL-1β in mice (**Coccia et al., 2012**). Interestingly, there was a significance difference (P < 0.05) in the expression levels of IL-1β between the two groups of UC. These data suggest that IL-1β could be used as a tool in the differentiation between the acute and chronic phases of UC.

Early studies have indicated that oxidative stress is one of the most important causative factors of UC (**Lee et al., 2010**). Oxygen species are produced in large amounts by infiltrating leukocytes in the inflamed mucosa and are crucial contributors to mucosal and, eventually, submucosal tissue destruction (**Rieder et al., 2007**). It is well known that Nrf2 signaling pathway is a defense system that mainly regulates the expression of antioxidant proteins in the body such as HO-1 and SOD to scavenge oxidants, thereby protecting cells from oxidative stress damage (**Mohan and Gupta,
The results of the current study showed that the expression level of Nrf2 in colon tissues of mice in ulcerative groups was significantly reduced and reached to its lowest level in the chronic UC group (Fig. 3C). The result obtained from the present study is in consistent with the finding of Trivedi and Jena who reported that exposure to DSS results in decreased expression of Nrf2 in mice (Trivedi and Jena, 2013).

In the current study SOD the downstream target of Nrf2 was estimated. We observed a depletion of enzymatic antioxidants in DSS-induced UC in mice where the level of SOD was significantly decreased in the acute and chronic DSS-induced UC (P < 0.01 and P < 0.001 respectively) (Fig. 4B). This finding indicated that treatment of mice with DSS lead to depletion of SOD and weakness of the anti-oxidant enzymatic defense system. Previous study revealed that animal model of DSS induced colitis showed a significant decrease in SOD activity in the colon, compared with the control group (Wang et al., 2019). An early study documented that the activity of SOD is increased in IBD pathogenesis as a reaction to protect the tissue against oxidative damage under the condition of inflammation and oxidative stress in IBD (Tian et al., 2017). In the present the low level of colonic SOD may be related to the low expression level of Nrf2.

It is proposed that NO is one of the possible etiological factors in the IBD (Kolios et al., 2004) and may be responsible for some of the overall effects of oxidative stress, including the release of cell contents and cell death, which cause tissue and organ damage (Kolios et al., 2004; Lee et al., 2010). In our study, a significantly increased level of NO was observed in DSS-induced UC in mice comparing to control group (P < 0.05) for acute UC and (P < 0.001) for chronic UC (Fig 4A). This finding indicated that DSS may induce colitis in mice partially through the enhancement of the production of NO; leading to colonic mucosal injury and cell death.

As a result of increased content of NO in colon tissues and the exhaustion of antioxidant enzyme SOD; the state of oxidative stress is enhanced and potentiate the inflammatory process in the colonic mucosa and development of UC. The present study revealed that the increased NF-κB expression level was accompanied by an increased in the expression level of IL-1β and colon tissue concentration of NO. Additionally, as a result of the low level of colonic Nrf2 the concentration of SOD in colon tissue was markedly decreased. This finding attractively reflects the central function of NF-κB and Nrf2 in the induction of UC via controlling of pro-inflammatory cytokines and oxidative stress levels. These data suggested that both of NF-κB and Nrf2 may be involved in the exacerbation of DSS-induced colitis and exert their destructive effect in the colonic mucosa partially through the induction of high expression of IL-1β, increasing the synthesis of NO and lowering the production of the cytoprotective SOD.

In conclusion, our data demonstrated that the alteration in NF-κB and Nrf2 pathways are contributed in the development of both the acute and chronic DSS-induced UC in mice and its effect may be largely due to its stimulation of IL-1β and NO production by NF-κB and diminished SOD production as a result of low Nrf2 expression. Therefore, any drugs that can inhibit NF-κB or enhance Nrf2 pathways...
might be a new and attractive preventive agent for UC. Additionally, the different in the expression levels of IL-1β among the acute and chronic UC making the prospect of using it as a diagnostic marker to differentiate between the acute and chronic UC is of interest.

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يشاركان في تطور التهاب 2 و العامل النووي المعتمق بعامل أريثرويد. العامل النووي كابا-بي الحادة والمزمن المستحث بواسطة ديكستران كبريتات الصوديوم في فئران القولون التقرحي التجربة

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المصطلحات:

التهاب القولون التقرحي هو مرض التهاب الأمعاء الذي يسبب التهاباً طويل الأمد وتقرحات في الجهاز الهضمي. وتنص النتائج على أن أدوية علاجات معقدة لاتزال غير واضحة حتى الآن. وقد تم في هذه الدراسة إحداث ميزة القولون التقرحي لدى الفئران وذلك بأعداد الفئران 3.5% من ديكستران كبريتات الصوديوم لمدة 7 أيام وذلك لإحداث التهاب القولون التقرحي الحاد بينما تم إعطاء 1.5% من ديكستران كبريتات الصوديوم لمدة أسبوع لأحداث التهاب القولون التقرحي المزمن. وكان النتائج من هذه الدراسة هو تحسين مستويات النجاح يائس لهذه الميزة. انخفاض مستويات الأملاح المفرط وفَلَع والالتهاب المزمن. وكان النتائج من هذه الدراسة هو تحسين مستويات النجاح يائس لهذه الميزة. انخفاض مستويات الأملاح المفرط وفَلَع والالتهاب المزمن.

الكلمات المفتاحية: ديكستران كبريتات الصوديوم. أدوية القولون التقرحي.

SOD IL-1β Nrf2 B1-NF