EFFECT OF DSS ADMINISTRATION AND SULFASALAZINE TREATMENT ON BODY WEIGHT AND OXIDATIVE STRESS IN EXPERIMENTAL ULCERATIVE COLITIS IN MICE

BY

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Abstract:

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD), characterized by chronic inflammation of the gastrointestinal tract. In general, IBD is more common in Western than in Eastern places, and in industrialized than in developing countries. However, the incidence of IBD has been rising recently in Eastern countries including Egypt. Symptoms of IBD include loss of appetite, tenesmus, abdominal cramps, diarrhea, and bloody stools. Available treatment options of IBD include drugs, surgery, or a combination of both. One of the most commonly used drugs for IBD management is an aminosalicylate called sulfasalazine. Several factors and symptoms of UC finally contribute to weight loss; thus, most of UC patients suffer from significant weight loss. The pathophysiology of IBD is complicated and involves several factors including immune, genetic, and environmental factors. Recently, a huge amount of research has concentrated on the role of oxidative stress in IBD, and several studies have proven that IBD patients suffer from excessive amounts of reactive oxygen species, while they have lower than normal amounts of antioxidant defenses. This leads to elevated amounts of oxidative stress-end products like malondialdehyde (MDA). In this study, we investigated body weight loss, histopathological alterations, and MDA levels in a mouse model of dextran sulfate sodium- induced UC, and the therapeutic effect of sulfasalazine. Our results showed that induction of colitis causes significant body weight loss and induces oxidative stress, and that treatment with sulfasalazine could restore normal mice body weights and combat the colitis-induced oxidative stress.

Keywords: ulcerative colitis, dextran sulfate sodium, sulfasalazine, body weight, histopathology, oxidative stress, malondialdehyde

Introduction:

Inflammatory bowel diseases (IBD) are a group of chronic inflammatory autoimmune disorders in which the colon and/or the small intestine become inflamed in a relapsing remitting fashion. There are several types of IBD, but the two most common types are Crohn's disease (CD) and ulcerative colitis (UC) (Podolsky, 2002). Since the middle of the twentieth century, the incidence of IBD began to rise in the Western industrialized countries like North America, Australia, and Europe, while it was still rare in Eastern developing countries (Molodecky *et al*., 2012). Over the past few decades, IBD incidence began to rise rapidly in Asia, South America, and the Middle East, although it is still lower than in Western countries (Sood *et al*., 2003; Ng *et al*., 2013; Ng, 2015). In Egypt, a study investigating IBD incidence from 1995 to 2009 showed a constant rise in the incidence of IBD, with UC being more common than CD (Esmat *et al*., 2014). Unfortunately, IBD is a lifelong disease that, until now, has no cure; available treatments only aim to induce and maintain remission (Amezaga and Van Assche, 2016). Currently available therapeutic interventions for IBD include drug management, surgical intervention, or a combination of both. According to the Crohn's and Colitis Foundation, five main drug classes are used in IBD management; aminosalicylates, corticosteroids, immunomodulators, antibiotics, and biologic therapies. Aminosalicylates, derivatives of 5-aminosalicylic acid (5-ASA), include several drugs, with sulfasalazine being the most common one, and considered the standard therapy in IBD (Garud and Peppercorn, 2009). Sulfasalazine is a prodrug that is broken in the

body to release 5-ASA, which is the active moiety (Scheline, 1973; Oz and Ebersole, 2008). IBD greatly influences the social and psychological status of patients, thus affecting their quality of life, as patients suffer from not only intestinal, but also systemic and emotional problems (Mitchell *et al*., 1988). One of the major concerns with IBD is the high risk of its development to colorectal cancer (CRC) (Kulaylat and Dayton, 2010). Symptoms of IBD vary depending on the severity of the disease and the site of inflammation. The World Gastroenterology Organisation has indicated the following symptoms for IBD; diarrhea, bloody stools, fever, fatigue, abdominal cramps and pain, loss of appetite, and weight loss. Several factors contribute to the weight loss associated with UC. Firstly, patients usually suffer from loss of appetite. In addition, food plays an important role in UC; UC patients could be advised by their doctors to eat some types of food and avoid others. The problem with food is that it usually triggers disease flare-ups. In order to avoid the undesirable symptoms that occur during flare-ups, some people tend to cut down their food intake or even stop eating, which leads to significant weight loss (Marchione, 2016).

Until now, the exact reason that causes a person to develop CD or UC is not fully understood, but the disease pathogenesis is known to be complicated and to involve several factors, including genetic, environmental, and immune factors (Mikhailov and Furner, 2009; Oberc and Coombes, 2015). It has been proposed that oxidative stress might be greatly involved in the pathogenesis of IBD (Borody *et al*., 2011), as prolonged and persistent inflammation is usually accompanied by increased production of reactive oxygen species (ROS) (Wendland *et al*., 2001). Normally, ROS are counteracted by

antioxidant defenses in the body, which include enzymatic antioxidants like superoxide dismutase and non-enzymatic antioxidants like reduced glutathione (Krinsky, 1992). Reactive oxygen species are released in excessive amounts in IBD patients and in animal models of IBD like dextran sulfate sodium (DSS)-induced UC (Boughton-Smith *et al*., 1993), and their levels are dependent on the severity of the colonic inflammation (Seril *et al*., 2003). Several factors contribute to the excessive production of ROS in IBD. For example, the aberrant activation of toll like receptor 4/ nuclear factor kappa B pathway in IBD leads to the overproduction of inflammatory cytokines that stimulate inflammatory cells to produce ROS as a response to inflammation (Coskun *et al*., 2011; Coskun *et al*., 2013; Pedersen *et al*., 2014). In addition, IBD patients usually have lower than normal levels of antioxidants (Kuroki *et al*., 1993; Kuroki *et al*., 1994). This oxidant/antioxidant imbalance leads to elevated amounts of ROS and increased oxidative stress. Reactive oxygen species tend to react with macromolecules like lipids, proteins, and DNA leading to their damage. One of the major end products of lipid peroxidation by ROS is malondialdehyde (MDA) (Halliwell, 1997). It has been found that MDA levels are elevated in UC and CD patients when compared to normal controls (Alzoghaibi *et al*., 2007). In this study, UC was induced in mice by cyclical administration of DSS and water. Body weights of mice were monitored throughout the study. After termination, colon samples were taken and preserved for histopathological investigation and scoring, and tissue MDA levels were determined.

Material and Methods:

Chemicals:

Dextran sulfate sodium (DSS, CAS no. 9011-18-1, molecular weight of approximately 40,000

Daltons) was purchased from TdB consultancy (Uppsala, Sweden). Sulfasalazine was purchased from El Qahera Company for Pharmaceutical and Chemical Industries (Cairo, Egypt). Malondialdehyde spectrophotometric kit was purchased from Biodiagnostics Company (Giza, Egypt).

Animals:

Male Swiss Albino mice, weighing approximately 25 g, were purchased from The Nile Company (Cairo, Egypt). During the studies, mice were housed in polystyrene cages and kept in the animal facility of Faculty of Pharmacy, Ain Shams University, under a constant temperature of 25 °C

and light/dark cycles (12:12 h). Mice were fed standard chow pellets *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, Ain Shams University.

Induction of UC and body weight monitoring:

The experiment lasted for 4 weeks. Animals were distributed into three groups, control, disease, and sulfasalazine-treated groups (n = 10). The control group received

pure drinking water for the whole period of the study, and was administered sulfasalazine vehicle, 0.5% sodium carboxymethylcellulose (Na CMC), orally by gavage starting from day 8 to the end of the study. Mice in the disease group were exposed to two alternating cycles of 3% DSS and water, each cycle for two weeks; 1 week DSS followed by 1 week water, to mimic the relapsing remitting course of chronic UC, i.e., they received 3% DSS in the drinking water during weeks 1 and 3, and pure drinking water during weeks 2 and 4. In addition, disease mice were administered 0.5% Na CMC starting from day 8 to the end of the study. Mice in the sulfasalazine-treated grou received 3% DSS in the drinking water during weeks 1 and 3, and pure drinking water during weeks 2 and 4, and were administered 100 mg/kg sulfasalazine suspended in 0.5% Na CMC (Wong *et al*., 2012; Xiao *et al*., 2015) starting from day 8 to the end of the study.

Every 7 days, i.e., on day 1 (first day), 8, 15, 22, and 29 (termination day), mice were weighed, their body weights were recorded, and body weight change was calculated as a percentage of the initial weight on day 1 as follows:

$$\text{Body weight change on day x (\%)} = \left(\frac{\text{Body weight on day x}}{\text{body weight on day 1}}\right) \times 100$$

On day 29, mice were anaesthetized and sacrificed by cervical dislocation.

Histopathological investigation and scorings:

On the last day of the study, after termination, colon tissue samples were withdrawn from the mice, fixed in 10% buffered formalin solution, and embedded in paraffin. Then, 5-µm paraffin embedded tissue sections were prepared from each block and stained with hematoxylin and eosin for histopathological investigation under the microscope. The severity of histopathological alterations was scored by an external investigator who was blind to the groups' identity.

Malondialdehyde (MDA) spectrophotometric determination:

Colon tissues were homogenized in phosphate-buffered saline to give a 10% tissue homogenate. The spectrophotometric assay was performed according to the manufacturer's instructions, and MDA concentration was calculated using the following equation:

$$\text{MDA tissue concentration } \left(\frac{\text{nmol}}{\text{g tissue}}\right) = \left(\frac{\text{A sample}}{\text{A standard}}\right) \times \left(\frac{10}{\text{tissue weight in grams}}\right)$$

Where A sample is the absorbance of the tissue homogenate (sample) at 534 nm, and A standard is the absorbance of the standard, which was prepared according to the kit protocol, at 534 nm.

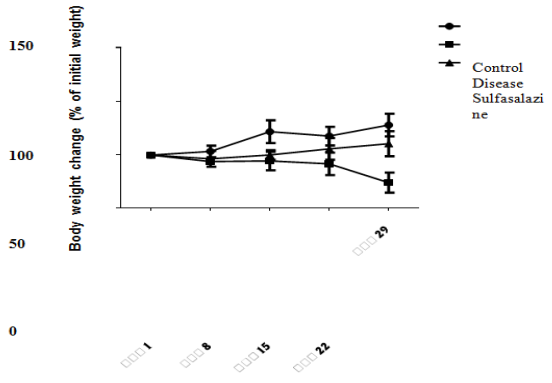
Statistical analysis:

Statistical analyses were performed using Graph Pad Instat software, version 3.05 (GraphPad Software, Inc. La Jolla, CA, USA). Graphs were plotted using Graph Pad Prism software, version 5.00 (Graph Pad Software, Inc. La Jolla, CA, USA). Body weight changes were analyzed using two-way analysis of variance (ANOVA) followed by Bonferroni post hoc test, while MDA results were analyzed by one-way ANOVA followed by Tukey's post hoc test. Results were considered statistically significant at $p < 0.05$. All data are represented as mean ± standard deviation (SD).

Results:

Ulcerative colitis-induced body weight loss and effect of sulfasalazine treatment:

Body weights of mice in the three groups were determined and recorded every 7 days, and body weight change was calculated as described in the Material and Methods. Our results demonstrated that induction of UC by DSS caused significant body weight loss. Several factors may have contributed to this weight loss; mice bled through their anus and suffered from 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. Sulfasalazine-treated mice demonstrated slight weight loss after the first week, but as treatment started with the beginning of the second week, they started to gain weight steadily to the end of the study. Until day 8, there was no significant difference between body weight changes in the control and disease groups, however, there was a significant difference between them on days 15, 22, and 29 ($p < 0.001$). Sulfasalazine treatment successfully ameliorated DSS-induced body weight loss, with significant



difference from the disease on days 22 ($p < 0.05$) and 29 ($p < 0.001$).

Body weight variations in the three groups throughout the study period are demonstrated in Figure1. Figure 1: Mean body weight changes of the control, disease, and sulfasalazine groups throughout the study period. Control, non-induced untreated mice; Disease, DSS-induced untreated mice; Sulfasalazine; DSS-induced mice treated with sulfasalazine. Data are represented as mean ± SD, n = 6 (two-way ANOVA followed by Bonferroni post hoc test).

Histopathological findings and scoring in the three experimental groups:

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 group show focal ulceration in the mucosal lining epithelium with underlying necrosis and inflammatory cell infiltration in the lamina propria, as well as crypt damage. In addition, the submucosa and the glandular structures between the lamina propria showed inflammatory cell infiltration and fibrosis. Surprisingly, treatment with sulfasalazine did not much improve the histological structure, as colon specimens from sulfasalazine-treated mice still showed focal ulceration, necrosis, and inflammatory cell infiltration, although less than that observed in the disease specimens. Histological findings of the three groups are shown in Figure 2, and histopatho logical scores are demonstrated in Table1.

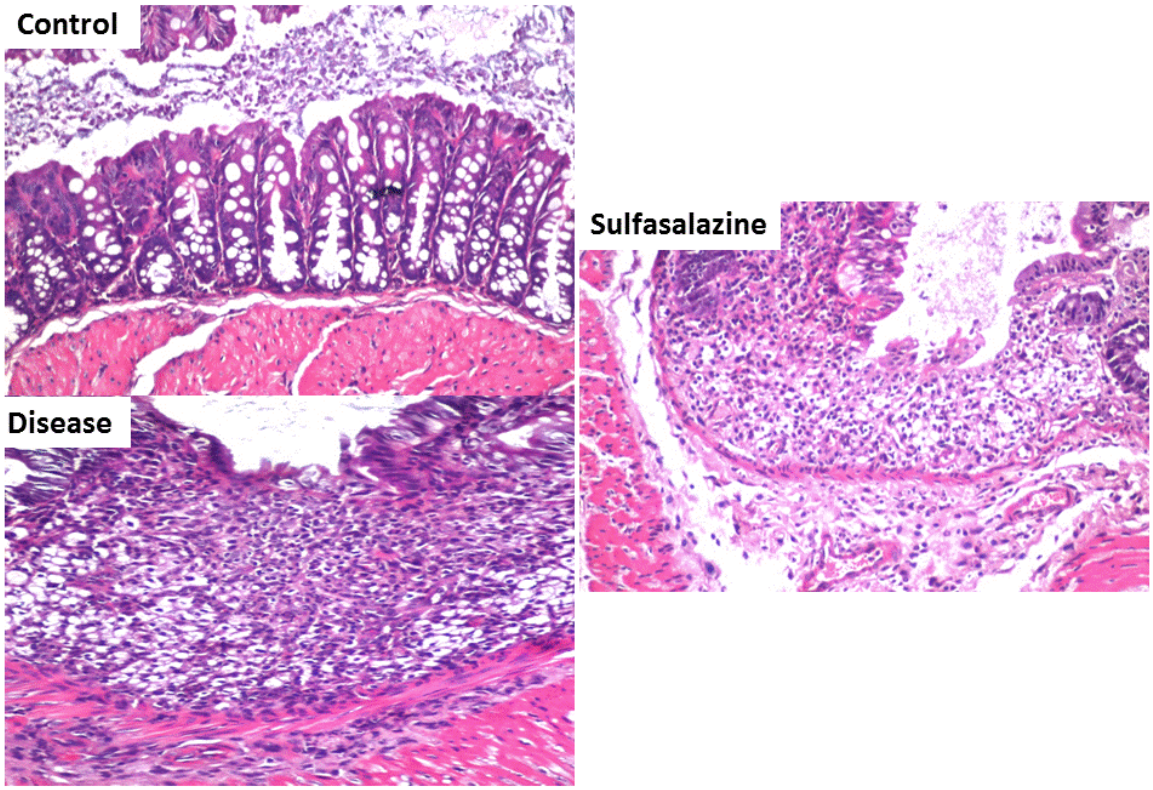


Figure 2: Representative images showing histological findings in control, disease, and sulfasalazine groups. Control, non-induced untreated mice; Disease, DSS-induced untreated mice; Sulfasalazine; DSS-induced mice treated with sulfasalazine. Original magnification × 400.

Histopathological scoring:

Table 1: The severity of histopathological alterations in control, disease, and sulfasalazine groups

Histopathological finding	Control	Disease	Sulfasalazine
Focal ulceration and necrosis in the mucosal layer	0	3	2
Inflammatory cell infiltration in submucosa	0	3	2
Mucosal fibrosis between glands in the lamina propria	0	2	1

Control, non-induced untreated mice; Disease, DSS-induced untreated mice; Sulfasalazine; DSS-induced mice treated with sulfasalazine; 0, nil histopathological alteration; 1, mild histopathological alteration; 2, moderate histopathological alteration; 3, severe histopathological alteration.

Effect of UC induction and sulfasalazine treatment on tissue MDA concentrations:

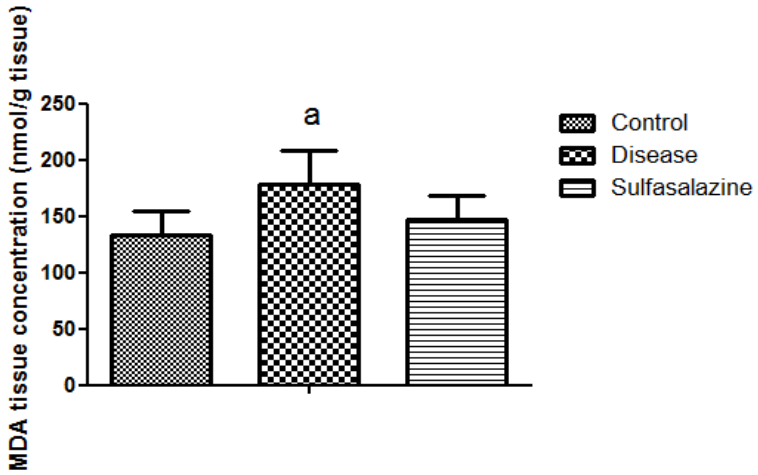
Tissue MDA concentrations in colon specimens from the three groups were determined using a spectrophotometric kit according to the manufacturer's instructions. Induction of UC caused a significant increase in the tissue MDA levels of the disease group as compared to the control group. Treatment with 100 mg/kg sulfasalazine reduced MDA levels to a lower level than that in the disease group, however, it was still higher than that in the control group, and did not differ significantly from any of them. Tissue MDA concentrations in samples from the three groups are shown in Table 2, and the difference between them is demonstrated in Figure 3.

Table 2: Tissue MDA concentrations in control, disease, and sulfasalazine groups (n = 6)

MDA concentration (nmol/g tissue)		
Control	**Disease**	**Sulfasalazine**
123.66	186.48	171.37
150.7	192.84	140.75
145.53	155.47	125.65
158.65	207.95	172.96
112.52	198.01	124.06
110.54	126.44	146.72

Control, non-induced untreated mice; Disease, DSS-induced untreated mice; Sulfasalazine; DSS-induced mice treated with sulfasalazine; MDA, malondialdehyde.

Figure 3: Effect of cyclical DSS administration and sulfasalazine treatment on tissue MDA concentrations. Control, non-induced untreated mice; Disease, DSS-induced untreated mice; Sulfasalazine; DSS-induced mice treated with sulfasalazine; [a], significantly different from control group at $p < 0.05$. Data are represented as mean ± SD, n = 6 (Data were analyzed by one- way ANOVA followed by Tukey's post hoc test).



Discussion:

Inflammatory bowel diseases are autoimmune diseases affecting the gastrointestinal tract. They are characterized by chronic relapsing remitting inflammation, which is accompanied by bleeding in the stools, and can eventually progress to CRC (Podolsky, 2002; Kulaylat and Dayton, 2010). The two most popular forms of IBD are UC and CD (Podolsky, 2002). Generally, the incidence of both UC and CD is higher in Western and industrialized countries than in Eastern and developing countries. However, their incidence in Eastern countries, including Egypt, is in a continuous state of increase (Sood *et al*., 2003; Molodecky *et al*., 2012; Ng *et al*., 2013; Esmat *et al*., 2014; Ng, 2015). Due to the abdominal pain and loss of appetite that are associated with IBD, in addition to the ability of food to trigger the symptoms, many IBD patients tend to cut down their food intake, which leads to considerable weight loss (Marchione, 2016). Several previous studies have demonstrated that weight loss occurs in association with different animal models of UC. For example, Motavallian-Naeini *et al*. showed that experimental rats treated with trinitrobenzene sulfonic acid (TNBS) demonstrated significant weight loss compared to control rats (Motavallian-Naeini *et al*., 2012). In addition, Tsai *et al*. showed that treatment of C57BL/6 mice with 2.5% DSS for 5 days, followed by 2 days of pure DSS-free water, resulted in significant weight loss compared to control mice who did not receive DSS at all (Tsai *et al*., 2015). This indicates that weight loss is associated with different models of UC; TNBS and DSS. In

this study, we investigated whether two cycles of DSS and water affect body weight. Our results showed that this model caused significant weight loss in the disease mice compared to the control mice. However, treatment with sulfasalazine significantly ameliorated DSS-induced body weight loss, where sulfasalazine-treated mice even gained weight at the end of the study. Ulcerative colitis is associated with abnormalities in the histological structure of the intestine like ulcerations, loss of crypt architecture, and inflammatory cell infiltration (Geboes, 2003). For example, Jeengar *et al*. induced colitis in mice by administration of 3.5% DSS in drinking water for 5 days, followed by 7 days of pure DSS-free water. Their histopathological investigation revealed that DSS-induced mice suffered from crypt destruction, a disturbed epithelial barrier, and severe inflammatory cell infiltration compared to the normal control group (Jeengar *et al*., 2017). In addition, Chassaing *et al*. indicated that chronic DSS-induced UC is associated with inflammatory cells, especially mononuclear leukocytes, infiltration, cry architectural changes, as well as deep mucosal lymphocytosis (Chassaing *et al*., 2014). In this study, we showed that induction of UC by DSS caused focal ulceration in the mucosal lining epithelium, underlying necrosis, inflammatory cell infiltration in the lamina propria, as well as crypt damage. In addition, the submucosa and the glandular structures between the lamina propria showed inflammatory cell infiltration and fibrosis. Treatment with sulfasalazine did not significantly improve the histological findings, but was associated with a decrease in the inflammatory cell infiltration. The pathogenesis of UC is complex and involves several factors. Recently, several studies have proposed that oxidative stress might play an important role in the development of IBD (Yan *et al*., 2015). For example, it was found that the levels of MDA, a major end product of lipid peroxidation resulting from high oxidative stress, are elevated in animal models of UC (Yao *et al*., 2010; Yan *et al*., 2015).

A previous study demonstrated that balsalazine, an aminosalicylate, significantly reduces DSS-induced elevation in MDA levels (Liu *et al*., 2009). Similarly, another study demonstrated that sulfasalazine significantly ameliorates DSS-induced elevation in MDA levels returning them to near-control levels (Farombi *et al*., 2013). In this study, we assessed MDA levels in the three groups, and found that induction of UC significantly elevated MDA levels compared to the control group, and that treatment with sulfasalazine lowered MDA levels to near-control levels, however, with no significant difference from the control or the disease groups.

In conclusion, induction of colitis by DSS administration caused significant body weight loss, histopathological alterations including ulcers and inflammatory cells' infiltration, and oxidative stress as indicated by the elevated MDA levels. Treatment of the mice with sulfasalazine significantly ameliorated DSS-induced body weight loss. It also lowered MDA levels, but with no significant difference from the disease group. However, sulfasalazine treatment did not significantly improve the histopathological signs of colitis.

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تأثير اعطاء ديكستران كبريتات الصوديوم و العلاج بالسلفاسالازين على وزن الجسم و الإجهاد التأكسدى فى التهاب القولون التقرحى المحدث تجريبيا فى الفئران

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[أ] قسم الأدوية و السموم، كلية الصيدلة، جامعة عين شمس، العباسية، القاهرة، مصر

نبذة مختصرة:

يعد التهاب القولون التقرحى نوعا من أنواع أمراض التهاب الأمعاء، يتميز بكونه التهاب مزمن فى الجهاز الهضمى. أمراض التهاب الأمعاء منتشرة فى الغرب أكثر من الشرق، و فى البلاد المتقدمة أكثر من البلاد النامية. و لكن، معدل انتشارها فى الدول الشرقية مثل مصر قد بدأ مؤخرا فى الازدياد. أعراض مرض التهاب القولون التقرحى تشمل انعدام الشهية، زحير، تقلصات فى البطن، إسهال، و براز دموى. أنواع العلاجات المتاحة لأمراض التهاب الأمعاء هى العلاج بالأدوية، او إجراء عملية جراحية، او الاثنان معا. أحد أكثر الأدوية استخداما فى علاج أمراض التهاب الأمعاء هم الأمينوساليسيليتس و أشهرهم السلفاسالازين. تشترك الكثير من أعراض التهاب القولون التقرحى فى أنها تؤدى الى فقدان الوزن، و يعانى كثير من المرضى من نقصان شديد فى الوزن. تعتبر الفسيولوجيا المرضية لأمراض التهاب الأمعاء معقدة جدا و تشمل الكثير من العوامل المناعية، الوراثية، و البيئية. مؤخرا، قامت الكثير من الأبحاث العلمية بالتركيز على دور الإجهاد التأكسدى فى أمراض التهاب الأمعاء، و أثبتت الكثير من الأبحاث أن مرضى التهاب القولون يعانون من وجود كميات هائلة من أنواع الأكسجين التفاعلية، و يعانون من نقصان فى كميات مضادات الأكسدة. كل هذا يؤدى الى زيادة فى كميات المنتجات النهائية للإجهاد التأكسدى مثل المالونداياًلديهايد. فى هذا البحث، قمنا باستكشاف نقصان الوزن ، التغيرات فى التشريح المرضى، و كميات المالونداياًلديهايد فى التهاب القولون التقرحى المحدث تجريبيا باستخدام ديكستران كبريتات الصوديوم فى الفئران، و التأثير العلاجى للسلفاسالازين. أظهرت نتائجنا أن إحداث التهاب القولون يؤدى الى نقصان شديد فى الوزن و إجهاد تأكسدى، و أن العلاج بالسلفاسالازين يستطيع أن يزيد أوزان الفئران و يقاوم الإجهاد التأكسدى الناتج عن التهاب القولون.

الكلمات الدالة: التهاب القولون التقرحى، ديكستران كبريتات الصوديوم، سلفاسالازين، وزن الجسم، التشريح المرضى، الإجهاد التأكسدى، مالونداياًلديهايد