RESEARCH ARTICLE

The Protective Effect of Cinnamic Acid against Ulcerative Colitis in Mice

Maysam A. Hussein*, Munaf H. Abdulrazzaq

Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Received: 25th December, 2022; Revised: 11th January, 2023; Accepted: 24th February, 2023; Available Online: 25th March, 2023

ABSTRACT

Objective: To study the protective effects of cinnamic acid on dextran sodium sulfate (DSS) induced ulcerative colitis (UC) in mice.

Materials and methods. Forty adult male mice were randomLy divided into five groups, control group, an induction group received 3% DSS in drinking water for 7 consecutive days. Two treatment groups received oral suspension of cinnamic acid 50 and 25 mg/kg, respectively and 3% DSS in drinking water, for 7 consecutive days. The final group received oral suspension of cinnamic acid 50 mg/kg for the latter 7 days without DSS in drinking water. All the animals were euthanized on day eight. The colon of animals was extracted and divided into two sections, the middle was homogenized and biochemically analyzed using the mean levels of total superoxide dismutase (SOD), and malondialdehyde, catalase, the distal for histopathological examination

Results: Total SOD, malondialdehyde, and catalase show significant results in the model group when compared to the control group. DSS with cinnamic acid 50 mg/kg group and DSS with cinnamic acid 25 mg/kg revealed a significant ($p < 0.05$) increase in total SOD and MDA and significant reduction in catalase when compared to the model group. Histopathological examination showed a significant reduction of inflammatory signs in all cinnamic acid-treated groups compared to the DSS model group.

Conclusion: The treatment with cinnamic acid significantly decreased the levels of DSS-associated oxidative stress. This finding supports the idea that the use of this substance could be used as a potential therapy for patients with ulcerative colitis.

Keywords: Inflammatory bowel diseases, Ulcerative colitis, Dextran sodium sulfate, Oxidative stress, Cinnamic acid.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.1.22

How to cite this article: Hussein MA, Abdulrazzaq MH. The Protective Effect of Cinnamic Acid against Ulcerative Colitis in Mice. International Journal of Drug Delivery Technology. 2023;13(1):143-149.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions that affect the gastrointestinal tract. They are often referred to as inflammatory bowel diseases. They are prevalent in developing countries and have an increased risk of developing colorectal cancer.[1-3]

The development of chronic and recurrent gastrointestinal tract inflammation known as UC is characterized by the loss of the colon's mucosal layer. This damage, which usually begins at the rectum, continues to affect the small intestine and, eventually the bowel wall. The other factors that contribute to this inflammation are the lack of proper function of immune system and the alteration of microbiota. The most common symptoms of UC include abdominal pain, chronic diarrhea, and bloody stool. It can also trigger weight loss.[4-6] Various factors such as the environment and the genetic factors that affect the immune system can also contribute to the development of UC. These factors can also decrease the body's antioxidant system's capacity and increase free radical production, including reactive oxygen species (ROS).[7,8]

Dextran sodium sulfate (DSS) is a type of chemical that can be used in animal models to induce the development and severity of colitis. It is a polysaccharide that is soluble in water and has a variable molecular weight from 5 to 1400 kDa. The most severe form of the disease, can be caused by the administration of up to 40–50 kDa in drinking water.[9]

The mechanism by which DSS induces inflammation is not clear. One possible explanation is that the damage to the lining of the large intestine allows the release of pro-inflammatory substances into the tissue beneath it.[10] An interaction between the immune system and the pathogenic microorganisms could also cause it. This interaction can trigger an inflammatory response and alter the function of the colonic system.[11-13]

In the treatment of patients with inflammatory bowel disease, such as UC, various anti-inflammatory medications are commonly used. These include steroids, aminosalicylates, and glucocorticoids. In severe cases, immune suppressants such as cyclosporine A are also commonly used.[14,15] Different lines of treatment for patients with UC, such as immunosuppressive drugs and antibiotics, can also have negative effects when

*Author for Correspondence: Ph.maysam09@gmail.com

used for a long-term treatment that limits their effectiveness. Because of their limited side effects, food derivatives have been integrated into the UC treatment.[16-18]

A type of fatty acid compound called cinnamic acid is made up of an acrylic acid group and a phenyl ring in trans-geometry. This aromatic compound has low toxicity and is an active moiety (a Michael acceptor)that can be used in the development of cancer drugs.[19] It can also be found in various other plants, such as ginseng and Chinese cinnamon. It can help protect against harmful effects of ultraviolet radiation and prevent the spread of pathogens. It also contributes to the development of the plant.[20,21] The term "cinnamon" refers to several cinnamomum species' sweet and spicy flavors. It can also be used as a food ingredient and improve its flavor. Its ability to remove bad breath has also been noted. It can also help improve the liver's ability to generate glucose. Its extract can also be used to treat various conditions.[22-24]

In Chinese medicine, cinnamon has been traditionally used to treat various conditions, such as inflammation and blood circulation disturbances. It can also help lower the risk of various diseases. It has been shown that it can have various pharmacological properties, such as antiulcerogenic, anti-inflammatory, and antimicrobial.[25,26]Aside from these, cinnamon can also help treat neuroinflammation and lower the risk of atherosclerosis. It can also help lower the blood pressure and cholesterol levels.[27,28]

In obese rats, cinnamon can decrease their bodyweight and prevent angiotensin-converting enzyme activity in serum. It can also help lower the risk of colon cancer. It can also treat various conditions, such as inflammation and blood circulation disturbances.[29,30] The coagulant effect of cinnamon can prevent bleeding. It can also help increase the blood circulation in the uterus and improve tissue regeneration. It can also be used as a tooth powder to treat various conditions, such as bad breath.[31-33]

MATERIALS AND METHODS

Ethics

Ethics approval for this study was obtained from the Ethics Committee of Baghdad University–College of pharmacology.

Chemicals and Kit

The chemical that was used in this work includes, diethyl ether (ROMAN pure chemistry, UK), formaldehyde 37% (Sinopharm chemical reagent Co., Ltd/China), dextran sodium sulfate (Med ChemExpress), poloxamer188 from (Thermo fisher scientific), cinnamic Acid(SIGMA-ALDRICH/ China), buffer solution (EuroClone S.p.A, Italy), distal water, mouse catalase (CAT) activity assays kit (Elabscience, China), mouse malondialdehyde (MDA) colorimetric assay kit (TBA Method) (Elabscience, China), mouse total superoxide dismutase (T-SOD) activity assay kit (Hydroxylamine Method) (Elabscience, China).

Animals

Forty adult male albino mice (aged 8 weeks) were included in this study, with weights ranging from 24–31 g. Mice were kept in standard conditions of temperature, day/night cycle, with free access to the standard diet. Dextran sodium sulfate dissolved in drinking water for seven days has been used to induce UC.

Experimental Protocol

Forty mice were divided into 4 groups, each group composed of 8 mice, as the following:

- Group I (Control group): Eight mice received distilling water and poloxamer (the suspending agent) suspension by oral gavage for 7 days.
- Group II (Model group): Eight mice received a suspension of distilling water and poloxamer (the suspending agent) by Oral gavage for 7 days. In addition to the administration of 3% DSS with drinking water during the seven days.
- Group III (cinnamic acid-model group): Eight mice received a suspension of 25 mg/kg of cinnamic acid by Oral gavage for 7 days. In addition to the administration of 3% DSS with drinking water during the seven days.
- Group IV (cinnamic acid-model group): Eight mice received an oral gavage suspension of 50 mg/kg of cinnamic acid for 7 days. In addition to the administration of 3% DSS with drinking water during the seven days.
- Group V (cinnamic acid-treated group): Eight mice received an oral gavage suspension of 50 mg/kg of cinnamic acid for 7 days.

The administration of cinnamic acid was done by oral route at the same time during the 7 days (9:00 am). Euthanization was done in the morning on the 8th day by using diethyl ether. Eight mice were sacrificed by cervical dislocation after anesthesia.

Preparation of DSS Working Solution

The 3% solution of DSS was prepared daily by dissolving 1.68 g of DSS in 56 mL distilled water (DW).

Preparation of Cinnamic acid Working Solution

For a dose of 50 mg of cinnamic acid, the stock solution was prepared as suspension with 100 mg of poloxamer.[34] The solution was then given to each mouse for seven day. A dose of 50 mg/kg (about 0.1 mL of the solution according to animal weight) was given orally by using a 1-mL syringe for each mouse for seven consecutive days.[35]

For a dose of 25 mg of cinnamic acid, the stock solution was prepared by as suspension with 100 mg of poloxamer. The solution was then given to each mouse for seven day. A dose of 25 mg/kg (about 0.1 mL of the solution according to animal weight) was given orally by using 1mL syringe for each mouse for seven consecutive days.

Isolation of the Colon

After euthanization on the 8th day, the colon was isolated and divided into three parts: the middle part was used for tissue homogenate to examine Antioxidant parameters, and the distal part was used for histopathological analysis.

Preparation of Colon Homogenate

The colon (distal part) has been washed and isolated using chilled phosphate buffer saline solution (PBS, pH 7.4) at 4 C to remove debris and excess blood. It was then weighed and

dried with filter paper. Each 100 mg of tissue was then placed in an Eppendorf tube containing 0.9 mL of chilled PBS.

The colon tissue was homogenized using a machine known as a homogenizer at speed three. After it was placed in an ice-filled beaker, the tissue was kept cold to prevent it from melting. The homogenate was then centrifuged at a temperature of 4°C and 3,000 rpm for 20 minutes. The supernatant was then isolated using a micropipette and stored at -20°C until the day of analysis.

Histopathological Examination of Colon Tissue

The distal colon was isolated and washed with normal saline. Tissue fixation was done by immersing the colon tissue in 10% formalin followed by a water bath. The colon was then dehydrated using increasing consecutive strengths of ethanol each 1-minute. The colon was then cleaned with xylene to eliminate alcohol and to provide the colon with some degree of transparency, then, the tissue was saturated with paraffin wax, heated, and blocked by pouring in embedded models. Blocks were cut by microtone into 5 µm, thick sections, washed in water bath, tissue was left in the oven for dewaxing, then stained with hematoxylin and eosin, and then examined using a light microscope by a pathologist.[36]

Measurement of Various Colon Injury Related Parameters

Quantitative Analysis of Total SOD

The paper presents the concept of the colorimetric method, a method of analysis involving the production of superoxide anion free radical (O2•-) by the xanthine and the xanthine oxidase reaction systems. Under the reaction of a developer, the O2•- oxidizes to form nitrite and turns purple. When the samples are analyzed with SOD, the superoxide anion free radical can be prevented using a spectrophotometer with a detection range of 4.7–166 U/mL.[37]

Quantitative Analysis of MDA

The kit included in this paper shows the level of lipid peroxidation and cellular damage that can be reflected in the content of the MDA. Through the use of the colorimetric method, the content of the MDA can be analyzed and detected. In the case of the lipid peroxide, the MDA can react with thiobarbituric acid and produce a red compound with an absorption peak of 532 nm. This compound can be produced using a spectrophotometer with a detection range of 0.38 to 133.33.[38]

Quantitative Analysis of CAT

The purpose of the colorimetric method is to analyze the reaction that occurs when catalase breaks down H_2O_2. After the ammonium molybdate has been used, the residual H_2O_2 reacts with ammonium molybdate to generate yellow complex. The activity of the CAT can be calculated by the output of the yellow complex, which is 405 nm, using a spectrophotometer with a detection range: 0.27–155.4 U/mL".[39]

Statistical Analysis

The data were analyzed using IBM SPSS statistics v25, means of groups were compared using one-way ANOVA followed by Post hoc (Tukey). All data are expressed as mean ± standard deviation SD and were considered as significant when the *p-value* < 0.05.

RESULTS

The effect of cinnamic acid administration on antioxidant markers in colon tissue homogenate for DSS-induced ulcerative colitis in mice is presented in Table 1 and Figures 1-3, which showed a significant decrease ($p < 0.05$) in total SOD levels, catalase level and significantly increased ($p < 0.05$) MDA level after DSS administration as compared with the distilled water control group. The pretreatment with cinnamic acid at a dose of 50mg/kg produced a significant increase ($p < 0.05$) in total SOD level, CAT level, and a significant reduction in MDA level as compared with the DSS model group. Furthermore, pretreatment with cinnamic acid 25 mg/kg also produce a significant reduction ($p < 0.05$) in total SOD levels, CAT levels, and a significant reduction in MDA levels as compared to the DSS model group.

Histopathology

Regarding the histological assessment of colon tissue for DSS-induced UC in mice, histological examination with hematoxylin and eosin (H and E) stain, the pathological changes in the colon tissue samples were examined in a blinded manner under an electronic microscope at x40 magnification for epithelial injury and infiltration of inflammatory mast cells. Figure 4A illustrates that the control group section shows a very small

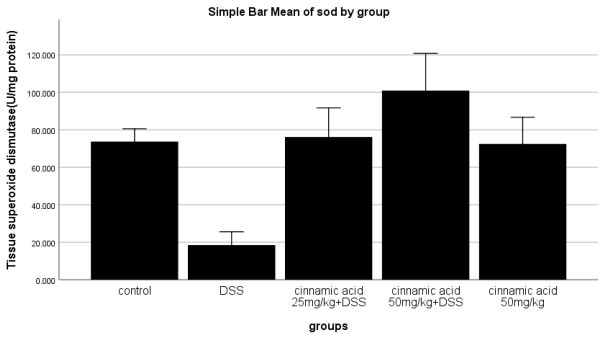

Figure 1: Effect of cinnamic acid on total sod levels in colon tissue homogenate for DSS-induced UC in mice.

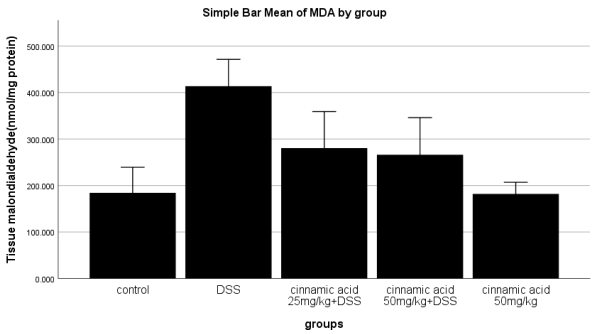

Figure 2: Effect of cinnamic acid on MDA levels in colon tissue homogenate for DSS-induced UC in mice.

Table 1: Effect of cinnamic acid administration on antioxidant markers in colon tissue homogenate for DSS-induced UC in mice

Group	*Level of total SOD (U/mg protein)*	*Level of MDA (nmol/mg protein)*	*Level of catalase (U/mg protein)*
Control group (n=8)	73.71± 8.16	184.25 ± 65.66	71.43 ± 8.52
DSS group (n=8)	18.49 ± 9.18*	413.65 ± 74.83 *	27.03 ± 18.54 *
DSS group + cinnamic acid 50 mg/kg (n=8)	76.17 ± 16.75 #	280.52 ± 84.98 #	73.33 ± 12.94 #
DSSgroup+cinnamicacid 25 mg/kg (n=8)	100.90 ± 21.43 #	266.080 ± 86.35#	89.21 ± 20.13 #
cinnamic acid 50 mg/kg (n=8)	72.42 ± 17.05	181.87 ± 29.96	70.50 ± 13.16

Each value is presented in (mean ± SD). * is significantly different compared with the control group ($p<0.05$). # is significantly different compared with the DSS group ($p<0.05$).

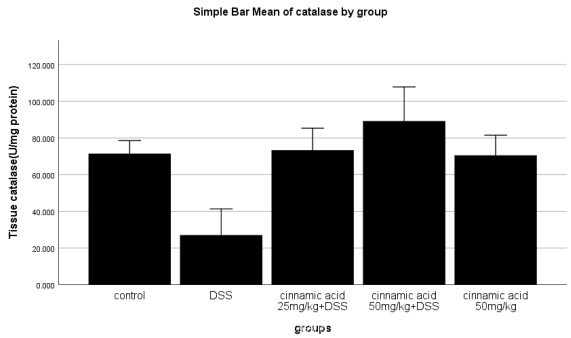

Figure 3: Effect of cinnamic acid on catalase levels in colon tissue homogenate for DSS-induced UC in mice.

number of inflammatory cells. At model DSS group section (Figure 4B) shows severe inflammatory cell infiltration, intact surface epithelium, colonic crypts, stroma, and submucosa in the control group contrary to branched crypts, cryptitis, decreased numbers of crypts and goblet cells, infiltration of inflammatory cells, and extensive submucosal. DSS with cinnamic acid 25 mg/kg group (Figure 4D) section showing mild inflammatory cells infiltration, and slight sloughing of surface mucosal epithelium. At (DSS + cinnamic acid 50 mg/kg) group (Figure 4C) section look like normal. Cinnamic acid 50 mg/kg only treatment section (Figure 4E) shows mild inflammatory cells infiltration.

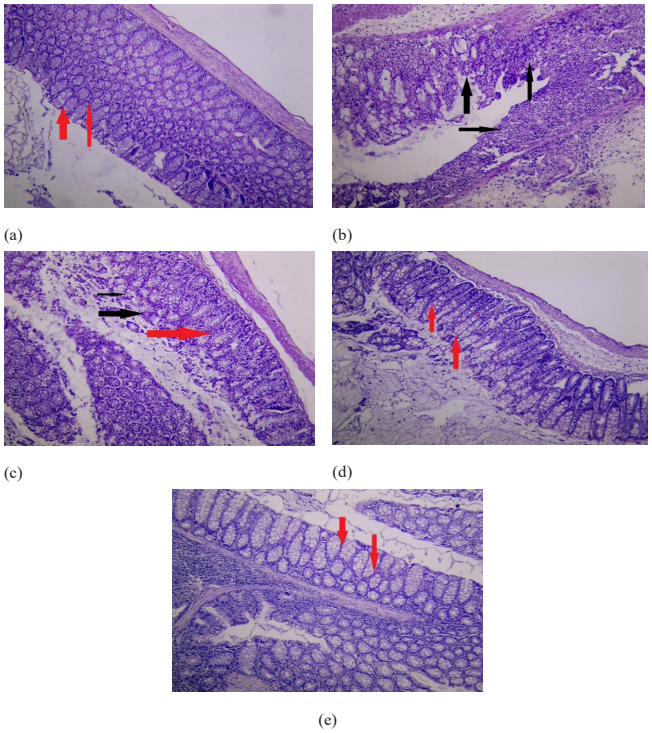

Figure 4: Effect of cinnamic acid-induced pathological colon changes. Red arrow: mucosa. Black arrow: sloughing of tissue (UC).

DISCUSSION

Cinnamic acid has been investigated for its possible beneficial effect on the colon and more specifically in the treatment of UC. As it was found its effect in the reduction of oxidative stress and epithelial cell damage prevention during the UC by either inhibition of lipid oxidation or their scavenging effect on free radicals such as superoxide anion.[40,41]

The induction of inflammation in the colon of animals has been used as an effective approach for studying the causes of IBD and developing new drugs. The sulfated polysaccharide DSS can disturb the epithelial cell barrier by affecting DNA replication, inhibiting epithelial cell overgrowth, activation of macrophages, increasing the release of cytokines, and breaking the balance of gut microflora.[42]

The activation of Th1 in acute phase of DSS-induced colitis is usually followed by activation of Th2 in the chronic phase. The tissue damage caused by this disease was mainly due to the presence of large amounts of IL-6 and TNF- α.[43] The pathological changes caused by this condition are similar to those seen in humans UC.[42,43]

Until now, no studies have been performed to determine the protective effect of cinnamic acid on DSS-induced UC. The colon morphological analysis of our experiment showed that the development of UC induced by DSS administration had been attenuated by cinnamic acid administration, assuming its antioxidant. Besides, biochemical analyzes were carried out to support the clinical study.

The immunological response caused by free radicals and the environment-induced damage are the main factors contributing to UC's development, in addition to genetic and oxidative stress. Other studies also suggest that the damaging effects of oxidative stress on the intestine play a major role and lead to UC's development.[44] As a result, effective Antioxidant therapy will be an important way to treat UC.[45,46] As a substance, SOD is known to be an effective antioxidant. It can

help the body remove free radicals from the environment and prevent them from wreaking further damage.[47]

In this study, the administration of DSS to the mouse resulted in UC evidenced by a significant increase in MDA level while causing a significant decrease in total SOD and CAT level which induced ulcerative colitis as compared to the control group.

The overproduction of ROS by ulcers has been linked to various diseases, such as atherosclerosis and cancer. This can also lead to colonic inflammation. In addition, the nitrogen species that are commonly used to attack DNA and tissue proteins can also lead to lipid peroxidation, which can affect antioxidant cellular capabilities.[48-50] The main components of an antioxidant defense against the production of ROS are either enzymatic like the SOD, glutathione peroxidase (GPx), and the CAT or non-enzymatic like glutathione.[51]

This study used DSS solution to induce UC as the DSS causes predominant tissue injury. In the comparison of the colonic tissue in the control group and the DSS induction group, MDA levels were elevated in the DSS induction group, as a result, the DSS solution was causing an increase in MDA due to oxidative stress in colonic tissue. MDA is the toxic product of lipid peroxidation secreted due to the toxic effects of active free oxygen radicals. It reflects the level of lipid peroxidation in the tissue; therefore, it is commonly used as a marker of lipid peroxidation.[52] Elevated MDA levels and lipid peroxidation in IBD and DSS induction groups have also been reported in other studies similar to this study.[53-55]

The properties of cinnamic acid as an antioxidant have been determined by its ability to inhibit the production of lipid oxidation and its scavenging activities against free radicals, such as superoxide anion.[40,56] The present study showed that cinnamic acid ameliorated the UC induced by DSS, evidenced by a significant decrease in the level of MDA level while causing a significant increase in total SOD and CAT levels.

"There are three mechanisms for antioxidant properties are reported in cinnamic acid during free radical scavenging. The first one involves a hydrogen atom being abstracted from the antioxidant by the radical. The second step involves the formation of a radical cation ArOH+_through the transfer of an electron to the free radical from the antioxidant and the deprotonation yielding ArO radical and ROH. In the last step, the phenolic compound is deprotonated and there is an electron transfer from the phenoxide anion to RO to yield phenoxyl radicals".[57] Studies have shown that the development of oxidative stress is caused by the imbalance between the prooxidant and the antioxidant systems toward the prooxidant system due to the excessive production of free oxygen radicals.[58]

SOD and CAT are other antioxidant markers that were measured in this study. Their levels decreased in the DSS induction group compared to the other groups. Both are endogenous antioxidants,[59] that protect cells from cytotoxic free oxygen radicals. "SOD is an important enzymatic antioxidant that plays a part in converting oxygen radicals into H_2O_2. H_2O_2 is subsequently detoxified by CAT and is converted into H_2O and O_2 molecules. Oxidative damage can be caused due to the release of ROS in IBD that disrupts the antioxidant system during mucosal inflammation. Decreased antioxidant levels have been revealed in patients with UC".[60,61]

The findings of this study support the idea that the injury caused by the presence of ROS in the tissue of patients with UC is a mechanism by which the antioxidant system weakens. It also shows that it significantly increases lipid peroxidation in the tissue.[62]

The study revealed that the treatment with cinnamic acid significantly decreased the levels of DSS-associated oxidative stress. This finding supports the idea that the use of this substance could be used as a potential therapy for patients with UC.

REFERENCES

1. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351):307–17.
2. Gasparetto M, Guariso G. Highlights in IBD epidemiology and its natural history in the paediatric age. Gastroenterol Res Pract. 2013;2013.
3. Dulai PS, Jairath V. Acute severe ulcerative colitis: latest evidence and therapeutic implications. Ther Adv Chronic Dis. 2018;9(2):65–72.
4. Toshifumi, HibiOgata H. Novel pathophysiological concepts of inflammatory bowel disease. J Gastroenterol. 2006;41(1):10–6.
5. Halling ML, Kjeldsen J, Knudsen T, Nielsen J, Hansen LK. Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases. World J Gastroenterol. 2017;23(33):6137.
6. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769–78.
7. Al-Rejaie SS, Abuohashish HM, Al-Enazi MM, Al-Assaf AH, Parmar MY, Ahmed MM. Protective effect of naringenin on acetic acid-induced ulcerative colitis in rats. World J Gastroenterol WJG. 2013;19(34):5633.
8. Lih-Brody L, Powell SR, Collier KP, Reddy GM, Cerchia R, Kahn E, et al. Increased oxidative stress and decreased antioxidant defenses in mucosa of inflammatory bowel disease. Dig Dis Sci. 1996;41(10):2078–86.
9. Okayasu I, Hatakeyama S, Yamada M, Ohkusa T, Inagaki Y, Nakaya R. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. Gastroenterology. 1990;98(3):694–702.
10. Chassaing B, Aitken JD, Malleshappa M, Vijay-Kumar M. Dextran sulfate sodium (DSS)-induced colitis in mice. Curr Protoc Immunol. 2014;104(1):15–25.
11. Cooper HS, Murthy SN, Shah RS, Sedergran DJ. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. Lab Invest. 1993;69(2):238–49.
12. Dieleman LA, Ridwan BU, Tennyson GS, Beagley KW, Bucy RP, Elson CO. Dextran sulfate sodium-induced colitis occurs in severe combined immunodeficient mice. Gastroenterology. 1994;107(6):1643–52.
13. Stepankova R, Powrie F, Kofronova O, Kozakova H, Hudcovic T, Hrncir T, et al. Segmented filamentous bacteria in a defined

bacterial cocktail induce intestinal inflammation in SCID mice reconstituted with CD45RBhigh CD4+ T cells. Inflamm Bowel Dis. 2007;13(10):1202–11.
14. Mahadevan U. Medical treatment of ulcerative colitis. Clin Colon Rectal Surg. 2004;17(01):7–19.
15. Lee HS, Park S-K, Park D Il. Novel treatments for inflammatory bowel disease. Korean J Intern Med. 2018;33(1):20.
16. Xu C-T, Meng S-Y, Pan B-R. Drug therapy for ulcerative colitis. World J Gastroenterol WJG. 2004;10(16):2311.
17. Głąbska D, Guzek D, Grudzińska D, Lech G. Influence of dietary isoflavone intake on gastrointestinal symptoms in ulcerative colitis individuals in remission. World J Gastroenterol. 2017;23(29):5356.
18. Rezayat SM, Dehpour A-R, Motamed SM, Yazdanparast M, Chamanara M, Sahebgharani M, et al. Foeniculum vulgare essential oil ameliorates acetic acid-induced colitis in rats through the inhibition of NF-kB pathway. Inflammopharmacology. 2018;26(3):851–9.
19. Wu Y, Wang M, Yang T, Qin L, Hu Y, Zhao D, et al. Cinnamic acid ameliorates nonalcoholic fatty liver disease by suppressing hepatic lipogenesis and promoting fatty acid oxidation. Evidence-Based Complement Altern Med. 2021;2021.
20. Ertle J, Dechêne A, Sowa J, Penndorf V, Herzer K, Kaiser G, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J cancer. 2011;128(10):2436–43.
21. Rocha LD, Monteiro MC, Teodoro AJ. Anticancer properties of hydroxycinnamic acids-a review. Cancer Clin Oncol. 2012;1(2):109–21.
22. Shareef AA. Evaluation of antibacterial activity of essential oils of Cinnamomum sp. and Boswellia sp. J Basrah Res. 2011;37(5):60–71.
23. Jakhetia V, Patel R, Khatri P, Pahuja N, Garg S, Pandey A, et al. Cinnamon: a pharmacological review. J Adv Sci Res. 2010;1(2):19–23.
24. Kwon H-K, Jeon WK, Hwang J-S, Lee C-G, So J-S, Park J-A, et al. Cinnamon extract suppresses tumor progression by modulating angiogenesis and the effector function of CD8+ T cells. Cancer Lett. 2009;278(2):174–82.
25. He Z-D, Qiao C-F, Han Q-B, Cheng C-L, Xu H-X, Jiang R-W, et al. Authentication and quantitative analysis on the chemical profile of cassia bark (cortex cinnamomi) by high-pressure liquid chromatography. J Agric Food Chem. 2005;53(7):2424–8.
26. Wang Y, Viscarra J, Kim S-J, Sul HS. Transcriptional regulation of hepatic lipogenesis. Nat Rev Mol cell Biol. 2015;16(11):678–89.
27. Szwajgier D, Borowiec K, Pustelniak K. The neuroprotective effects of phenolic acids: molecular mechanism of action. Nutrients. 2017;9(5):477.
28. Zang L-Y, Cosma G, Gardner H, Shi X, Castranova V, Vallyathan V. Effect of Antioxidant protection by p-coumaric acid on low-density lipoprotein cholesterol oxidation. Am J Physiol Physiol. 2000;279(4):C954–60.
29. Mnafgui K, Derbali A, Sayadi S, Gharsallah N, Elfeki A, Allouche N. Anti-obesity and cardioprotective effects of cinnamic acid in high fat diet-induced obese rats. J Food Sci Technol. 2015;52(7):4369–77.
30. Wondrak GT, Villeneuve NF, Lamore SD, Bause AS, Jiang T, Zhang DD. The cinnamon-derived dietary factor cinnamic aldehyde activates the Nrf2-dependent Antioxidant response in human epithelial colon cells. Molecules. 2010;15(5):3338–55.
31. Hossein N, Abolfazl M, Mahdi S, Ali K. Effect of Cinnamon zeylanicum essence and distillate on the clotting time. J Med Plants Res. 2013;7(19):1339–43.
32. Rao PV, Gan SH. Cinnamon: a multifaceted medicinal plant. Evidence-Based Complement Altern Med. 2014;2014.
33. Aneja KR, Joshi R, Sharma C. Antimicrobial activity of Dalchini (Cinnamomum zeylanicum bark) extracts on some dental caries pathogens. J Pharm Res. 2009;2(9):1387–90.
34. Fischer SM, Parmentier J, Buckley ST, Reimold I, Brandl M, Fricker G. Oral bioavailability of ketoprofen in suspension and solution formulations in rats: the influence of poloxamer 188. J Pharm Pharmacol. 2012;64(11):1631–7.
35. Patra K, Bose S, Sarkar S, Rakshit J, Jana S, Mukherjee A, et al. Amelioration of cyclophosphamide induced myelosuppression and oxidative stress by cinnamic acid. Chem Biol Interact. 2012;195(3):231–9.
36. Jabbar AASA, Kathem SH. The Protective Effect of Mentha spicata Ethanolic Extract on Irinotecan-Induced Mucositis in Mice. Iraqi J Pharm Sci. 2019;28(1).
37. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem. 1972;247(10):3170–5.
38. Heath RL, Packer L. Photoperoxidation in isolated chloroplasts: I. Kinetics and stoichiometry of fatty acid peroxidation. Arch Biochem Biophys. 1968;125(1):189–98.
39. Sinha AK. Colorimetric assay of catalase. Anal Biochem. 1972;47(2):389–94.
40. Zhao C, Zhang L, Wang H, HUANG D. Study on Anti-oxidation Effects of Cinnamic Acid and Its Derivants. Food Sci. 2005;26:218–22.
41. Kancheva VD. Phenolic antioxidants–radical-scavenging and chain-breaking activity: A comparative study. Eur J Lipid Sci Technol. 2009;111(11):1072–89.
42. Mizoguchi A. Animal models of inflammatory bowel disease. Prog Mol Biol Transl Sci. 2012;105:263–320.
43. Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. Annu Rev Immunol. 2002;20(1):495-549.
44. Jin X, Chen D, Zheng R-H, Zhang H, Chen Y-P, Xiang Z. miRNA-133a-UCP2 pathway regulates inflammatory bowel disease progress by influencing inflammation, oxidative stress and energy metabolism. World J Gastroenterol. 2017;23(1):76.
45. Boeing T, de Souza P, Bonomini TJ, Mariano LNB, Somensi LB, Lucinda RM, et al. Antioxidant and anti-inflammatory effect of plumieride in dextran sulfate sodium-induced colitis in mice. Biomed Pharmacother. 2018;99:697–703.
46. Kim K-J, Park J-M, Lee J-S, Kim YS, Kangwan N, Han Y-M, et al. Oligonol prevented the relapse of dextran sulfate sodium-ulcerative colitis through enhancing NRF2-mediated antioxidative defense mechanism. J Physiol Pharmacol. 2018;69(3).
47. Younus H. Therapeutic potentials of superoxide dismutase. Int J Health Sci (Qassim). 2018;12(3):88.
48. Fresco P, Borges F, Diniz C, Marques MPM. New insights on the anticancer properties of dietary polyphenols. Med Res Rev. 2006;26(6):747–66.
49. Tüzün A, Erdil A, İnal V, Aydın A, Bağcı S, Yeşilova Z, et al. Oxidative stress and Antioxidant capacity in patients with inflammatory bowel disease. Clin Biochem. 2002;35(7):569–72.
50. Tahan G, Aytac E, Aytekin H, Gunduz F, Dogusoy G, Aydin S, et al. Vitamin E has a dual effect of anti-inflammatory and antioxidant activities in acetic acid–induced ulcerative colitis in rats. Can J Surg. 2011;54(5):333.

51. Bertevello PL, Logullo ÂF, Nonogaki S, Campos FM, Chiferi V, Alves CC, et al. Immunohistochemical assessment of mucosal cytokine profile in acetic acid experimental colitis. Clinics. 2005;60(4):277–86.
52. Kaya E, Gür ES, Özgüç H, Bayer A, Tokyay R. L-glutamine enemas attenuate mucosal injury in experimental colitis. Dis colon rectum. 1999;42(9):1209–15.
53. Alzoghaibi MA, Al Mofleh IA, Al-Jebreen AM. Lipid peroxides in patients with inflammatory bowel disease. Saudi J Gastroenterol. 2007;13(4):187.
54. DS PB, Medhi B, Prakash A, Chakrabarti A, Vaiphei K, Khanduja KL. Comparative evaluation of different doses of PPAR-γ agonist alone and in combination with sulfasalazine in experimentally induced inflammatory bowel disease in rats. Pharmacol Reports. 2013;65(4):951–9.
55. Gul M, Kayhan B, Elbe H, Dogan Z, Otlu A. Histological and biochemical effects of dexmedetomidine on liver during an inflammatory bowel disease. Ultrastruct Pathol. 2015;39(1): 6–12.
56. Cos P, Rajan P, Vedernikova I, Calomme M, Pieters L, Vlietinck AJ, et al. In vitro Antioxidant profile of phenolic acid derivatives. Free Radic Res. 2002;36(6):711–6.
57. Mazzone G, Russo N, Toscano M. Antioxidant properties comparative study of natural hydroxycinnamic acids and structurally modified derivatives: Computational insights. Comput Theor Chem. 2016;1077:39–47.
58. Halliwell B, Chirico S. Lipid peroxidation: its mechanism, measurement, and significance. Am J Clin Nutr. 1993;57(5):715S-725S.
59. Flora G, Gupta D, Tiwari A. Toxicity of lead: a review with recent updates. Interdiscip Toxicol. 2012;5(2):47.
60. Krzystek-Korpacka M, Neubauer K, Berdowska I, Zielinski B, Paradowski L, Gamian A. Impaired erythrocyte Antioxidant defense in active inflammatory bowel disease: impact of anemia and treatment. Inflamm Bowel Dis. 2010;16(9):1467–75.
61. D'Odorico R. Cardin, R. D'Inca', D. Martines, A. Ferronato, GC Sturniolo, A SB. Reduced plasma Antioxidant concentrations and increased oxidative DNA damage in inflammatory bowel disease. Scand J Gastroenterol. 2001;36(12):1289–94.
62. Nieto N, Torres MI, Fernandez MI, Giron MD, Rios A, Suarez MD, et al. Experimental ulcerative colitis impairs Antioxidant defense system in rat intestine. Dig Dis Sci. 2000;45(9): 1820–7.