Effectiveness of *Ricinus communis* root extract against dextran sodium sulfate induced ulcerative colitis in rats

Musaratafrin Saiyed¹, Punam Sachdeva¹, Mona Kukkar²

¹Department of Pharmacology, A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar - 388120, Gujarat, India, ²Department of Pharmacognosy, A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar - 388120, Gujarat, India

Abstract

**Introduction:** Ulcerative colitis (UC) is an idiopathic, autoimmune, and inflammatory disorder which affects the lining of the colon and the rectum. It involves inflammatory mediators such as cytokines, nitrogen and oxygen-derived free radicals exerting oxidative stress, deranged colonic milieu, and increase in intestinal permeability. *Ricinus communis* roots are used traditionally in diseases of liver and rectum, in gastropathy such as constipation, inflammation, fever, colic and in colon cancer. Several reports exhibiting analgesic, antibacterial, anti-inflammatory, and antioxidant activity of *R. communis* root extract (RCRE) are available. Hence, this study was undertaken with the objective to evaluate the effectiveness of RCRE in dextran sodium sulfate (DSS) induced UC in rats. **Materials and Methods:** A total of 30 Sprague-Dawley rats were divided into five groups (*n* = 6). 5- Aminosalicylic acid was used as a standard drug, and RCRE was administered at a dose of 250 mg/kg and 500 mg/kg p.o. for 14 days. UC was induced by replacing drinking water with 4% DSS solution for the past 7 days. **Results:** Severity of colitis induced was assessed by observing macroscopic and microscopic characteristics and changes in the level of oxidative stress parameters. All parameters were altered in model control rats, while pre-treatment with RCRE preserved normal colonic architecture, improved macroscopic and microscopic scores and altered oxidative stress biomarkers in the colon. **Conclusion:** Results showed the good effectiveness of RCRE against DSS-induced UC possibly by its anti-inflammatory and antioxidant activity.

**Key words:** Anti-inflammatory, dextran sodium sulfate, oxidative stress, *Ricinus communis* root extract, ulcerative colitis

**INTRODUCTION**

Ulcerative colitis (UC) is an idiopathic, autoimmune, and inflammatory disorder of colon/bowel.[¹] It is an inflammatory disease that affects the lining of the colon and the rectum. Pathological findings associated with UC are increased in certain inflammatory mediators including cytokines, nitrogen and oxygen-derived free radicals exerting oxidative stress, deranged colonic milieu, and increase in intestinal permeability.[²,³] Excessive production of nitric oxide (NO) by inducible NO synthetase in chronic colitis may be detrimental to the integrity of mucosa based on generation of reactive nitrogen species (RNS) which causes cellular degeneration in various tissues contributing to the development of intestinal damage, plasma, and mucosal prostaglandin rise simultaneously with degree of colonic injury.[⁴,⁵] It is treated using anti-inflammatory drugs, oral steroids, immune suppressants, antibiotics, and anti-tumor necrosis factor-α drugs.[⁶] All these drugs are typically associated with side effects which limit their usefulness. Plants are considered to be a goldmine to tackle complex inflammatory conditions with minimum side effects. Various plants are also reported to be useful in IBD due to their immune modulatory antiulcerogenic property and anti-inflammatory property.[⁶-¹⁰] The plant *Ricinus communis* belongs to the family Euphorbiaceae. It is also known as castor in English, erand in Hindi, erendo and ereandi in

**Address for Correspondence:**
Musarat Saiyed, 14/A, Saiyad Nagar, Juna Bazaar, Miyagam Karjan - 391240, Vadodara, Gujarat, India.
Phone: +91-9408710393.
E-mail: musaratsaiyed@yahoo.com

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Guajarati. It is a tropical plant distributed widely across the world.[11] Root part of *R. communis* is traditionally claimed as anti-inflammatory for diseases of liver, spleen, pile disorders, diseases of rectum, in gastropathy such as constipation, inflammation, fever, colic and in colon cancer.[12-14] It is also used orally for arthritis and sciatica and as an antipyretic and analgesic.[14] *R. communis* root extract is reported to possess analgesic,[15,16] antibacterial,[17] anti-inflammatory, and antioxidant activity.[18,19] 2-5% dextran sodium sulfate (DSS) in drinking water causes hyperemia, ulceration and submucosal edema of the colon, resulting in softening of stool with hemoccult, which symptomatically resembles UC in man.[20-23] Thus, a hypothesis was generated that, a root extract of *R. communis* may be effective in the treatment of UC, which is an inflammatory disease of the bowel/colon with oxidative stress as the main etiology. Literature survey shows that root part of *R. communis* has not been investigated for its effectiveness in UC. Hence, this study was undertaken with the aim of evaluation of *R. communis* root extract (RCRE) in DSS-induced UC in rats.

**MATERIALS AND METHODS**

**Drugs and Chemicals**

5- Aminosalicylic acid (5-ASA) procured from Sigma-Aldrich, DSS purchased from MP Biomedicals, Mumbai, India were used for the study. All other chemicals and reagents used were of analytical grade.

**Animals**

Male Sprague-Dawley rats with an average weight of 200 g were procured from Zydus Research Centre, Ahmedabad. The animals were housed in polypropylene cages at 25±2°C temperature with a relative humidity of 45-55% under 12:12 light - dark cycles. They were fed with standard laboratory animal feed and water *ad libitum*. The experimental protocol (Protocol no: CPCSEA/IAEC/ARCP/2015-2016/02) was approved by the Institutional Animal Ethics Committee (IAEC) of A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar, Gujarat, and all experiments were carried out as per CPCSEA guidelines.

**Preparation of the Extract**

The roots of the plant *R. communis*, Family - Euphorbiaceae were collected from Karjan, District Vadodara, Gujarat and identified and authenticated (Authentication no: AAU/BACA/SST/SSN/215/16) by Dr. Sasidharan N., Head, Department of Seed Science and Technology, B. A. College of Agriculture, Anand, Gujarat. A voucher specimen of the plant is deposited in the botany herbarium of A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar (Herbarium no: MS/RC-01/30/ARGH-16).

Collected roots of the plant were chopped, shade dried and coarsely powdered. The powder was defatted with petroleum ether (60-80°C) and extracted with methanol using Soxhlet Extractor. The extract was dried.[18] The percentage yield of the extract obtained was 4.2% (w/w). The extract was stored in airtight container at 2-5°C for further experimental use.

Doses equivalent to 250 and 500 mg/kg body weight were calculated and suspended in 0.5% carboxymethyl cellulose (CMC) solution for the experiment.

**Preliminary Phytochemical Screening**[24]

RCRE was subjected to preliminary phytochemical screening of extract to detect the presence of various active phytoconstituents.

**Induction of Colitis in Rats**

Colitis was induced in rats by replacing drinking water with 4% DSS solution orally for the past 7 days of 21 days treatment period.[6,20-22,25-27]

**Grouping of Animals and Dose Schedule**

A total of 30 Sprague-Dawley rats were randomly divided into five groups with six animals in each group. Group I (normal control group) received vehicle (0.5% CMC [1 ml/kg] p.o.) for 3 weeks (21 days). Group II (model control group) received vehicle (0.5% CMC [1 ml/kg] p.o.) for 2 weeks (14 days) followed by 4% DSS in drinking water in the last week (7 days). Group III received 5-ASA (500 mg/kg) p.o. once daily for 14 days. Groups IV and V received RCRE (250 mg/kg and 500 mg/kg p.o., respectively) for 14 days. On day 15, oral administration of 5-ASA and RCRE to Groups III-V was stopped, and intrarectal administration of 5-ASA, RCRE (250 mg/kg), and (500 mg/kg), respectively, was started. Simultaneously colitis was induced in Groups III-V by replacing drinking water with 4% DSS solution for the past 7 days (3rd week). On day 21, rats were sacrificed under anesthesia. The distal 10 cm portion of the colon of all animals of all groups was removed, cut longitudinally, cleaned and used for macroscopic scoring and histopathological scoring. Furthermore, colon length, colon weight, colon weight/length ratio, and oxidative stress parameters were measured.[27]

**Assessment of Colitis**

**Body weight**

Body weight of all animals of all groups was recorded on every alternate day and change in body weight at the weekly interval was calculated and documented.[29]
**RESULTS**

**Preliminary Phytochemical Screening of RCRE**

The preliminary phytochemical screening of methanolic extract of RCRE using standard chemical tests was found to contain carbohydrates, glycosides, saponins, flavonoids, alkaloids, tannins, and phenolic compounds.

**Effect of RCRE on Body Weight**

Body weight of animals in all groups increased up to 14 days (2 weeks). In the 3rd week, in model control group increase in body weight was significantly less \( (P < 0.0001) \) due to induction of colitis. Pre-treatment of rats with 5-ASA (500 mg/kg) and RCRE (250 and 500 mg/kg p.o.) for 14 days, significantly increased \( (P < 0.001) \) body weight as compared to DSS-treated model control rats [Figure 1].

**Effect of RCRE on Stool Consistency**

Induction of colitis by use of 4% DSS resulted in significant increase \( (P < 0.001) \) in stool consistency score in model control rats as compared to score of normal rats. 14 days pre-treatment of rats with 5-ASA and RCRE (500 mg/kg) significantly decreased \( (P < 0.05) \) stool consistency score as compared to score of model control rats. RCRE (250 mg/kg) also reduced stool consistency score, but the difference was not found to be significant [Figure 2].

**Effect of RCRE on Morphological Characteristics and Macroscopical Score**

Replacing drinking water by 4% DSS for the past 7 days (3rd week) induced colitis of varying severity. Inflammatory reaction in the colon was evidenced by focal hyperemia, bowel wall thickening, and inflammation along the length of the colon. Colon of 5-ASA and RCRE treated groups showed signs of suppression of inflammatory reaction with mild lesions [Figure 3].

The mean macroscopical score in model control rats was significantly higher \( (P < 0.01) \) as compared to normal control rats. Pre-treatment with 5-ASA and RCRE (250 and 500 mg/kg) (500 mg/kg) in rats for 14 days, significantly \( (P < 0.01) \) and dose-dependently decreased macroscopic score as compared to DSS-treated model control rats [Table 1].

**Effect of RCRE on Microscopical Score**

As compared to normal control group, the mean microscopically score in model control rats was significantly increased \( (P < 0.001) \). The 14 days pre-treatment with 5-ASA prevented mucosal damage and significantly decreased \( (P < 0.05) \) mean microscopically score when compared to normal control group.

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**Stool consistency**

Stool consistency of all animals of all groups was observed daily and scored on a scale ranging from 0 to 3 as follows: (0) Normal stool, (1) soft stool but still formed, (2) very soft stool, and (3) diarrhea. \(^{[29]}\)

**Macroscopic score**

Isolated colons were examined for signs of inflammation by an independent blind observer. Severity of inflammation was observed macroscopically and scored according to scale ranging from 0 to 10 as follows: (0) No damage, (1) focal hyperemia, (2) ulceration without hyperemia or bowel wall thickening, (3) ulceration with inflammation at 1 site, (4) 2 sites of ulceration and inflammation, (5) major sites of inflammation >1 cm along the organ, and (6-10) major sites of inflammation >2 cm along the organ. \(^{[29]}\)

**Microscopical analysis**

Colons of all animals of all groups were removed, rinsed with phosphate-buffered saline (PBS, pH 7.4) and opened longitudinally. Colon was immersed immediately in neutral buffered 10% formalin, embedded in paraffin and incubated overnight at 4°C. After incubation colon was cut into 5 mm cross sections. The cross sections of colon were stained using Hematoxylin and Eosin stain and were interpreted in a blinded manner by a pathologist using scale ranging from 0 to 4 as follows: (0) No evidence of inflammation, (1) low level of inflammation with scattered infiltrating mononuclear cells, (2) moderate inflammation with multiple foci, (3) high level of inflammation with increased vascular density and marked wall thickening, and (4) maximal severity of inflammation with transmural leukocyte infiltration and loss of goblet cells. \(^{[29]}\)

**Oxidative stress biomarkers**

Remaining portion of the colon was used for assessment of myeloperoxidase (MPO), malondialdehyde (MDA), no level, and superoxide dismutase activity (SOD). MPO activity was calculated by finding out the ratio of change in absorbance and molar extinction coefficient for O-dianisidine. \(^{[27]}\) Lipid peroxidation was evaluated by measuring MDA using the thiobarbituric acid method described by Marquez, 2010 and expressed as nmols of MDA/mg protein. NO level in the colon was measured using the standard curve of 0.001M sodium nitrite in water and reported as nmols/mg protein. \(^{[30]}\) SOD activity was determined and expressed as WU/mg of protein. \(^{[31]}\)

**Statistical Analysis**

All data are expressed as mean±standard error of mean of six rats per experimental group. Statistical analysis was performed using Instat GraphPad 3.0 statistical software. All parametric data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett’s test. All non-parametric data were analyzed by non-parametric ANOVA followed by Friedman test. \( P < 0.05 \) was considered as statistically significant.
model control group. Similar results were obtained with RCRE (250 and 500 mg/kg) treated groups, where mucosal damage and inflammation was prevented by RCRE resulting in significant and dose-dependent reduction ($P < 0.05$) in the mean microscopical score when compared with DSS-treated model control rats [Table 1 and Figure 4].

**Effect of RCRE on Colon Length, Colon Weight**

Mean colon length and colon weight in DSS-treated model control rats were significantly increased ($P < 0.01$) as compared to normal rats suggesting induction of colitis by DSS. Comparing DSS-treated model control rats with RCRE (500 mg/kg) treated rats, the increase in mean colon length was significantly less ($P < 0.05$). Furthermore, significantly less increase in colon weight was observed in RCRE (250 and 500 mg/kg) treated rats as compared to model control rats ($P < 0.05$ and $P < 0.01$, respectively). Similar results were observed in rats pre-treated with 5-ASA (500 mg/kg) ($P < 0.01$) [Table 1].

**Effect of RCRE on Colon Weight to Length Ratio**

Colon weight to length ratio in model control rats increased due to induction of colitis by DSS. Pre-treatment of rats with 5-ASA (500 mg/kg) and RCRE (250 and 500 mg/kg) for 14 days decreased colonic weight to length ratio as compared to DSS-treated model control rats. However, the difference was not found to be statistically significant [Table 1].

**Effect of RCRE on Levels of Oxidative Stress Parameters**

MPO content and NO level in DSS-treated model control rats were significantly ($P < 0.0001$) increased as compared normal rats. The 14 days pre-treatment with 5-ASA (500 mg/kg) and RCRE (250 mg/kg and 500 mg/kg p.o.) significantly
**Table 1:** Effect of RCRE (250 and 500 mg/kg) and 5-ASA (500 mg/kg) on colonic macroscopic score, microscopical score, colon length, colon weight, and weight to length ratio

<table>
<thead>
<tr>
<th>Groups</th>
<th>Macroscopic score</th>
<th>Microscopical score</th>
<th>Colon length</th>
<th>Colon weight</th>
<th>Colon Wt/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>0</td>
<td>0</td>
<td>8.78±0.24</td>
<td>0.94±0.07</td>
<td>0.107±0.01</td>
</tr>
<tr>
<td>Model control</td>
<td>7.3±0.42**</td>
<td>2.5±1.02**</td>
<td>11.8±0.36**</td>
<td>1.36±0.10**</td>
<td>0.115±0.104</td>
</tr>
<tr>
<td>5-ASA (500 mg/kg)</td>
<td>1.83±0.30**</td>
<td>0.5±0.20**</td>
<td>9.03±0.30**</td>
<td>1.01±0.02**</td>
<td>0.111±0.004</td>
</tr>
<tr>
<td>RCRE (250 mg/kg)</td>
<td>2.5±0.34**</td>
<td>1.5±0.61</td>
<td>10.8±0.40</td>
<td>1.07±0.04**</td>
<td>0.106±0.004</td>
</tr>
<tr>
<td>RCRE (500 mg/kg)</td>
<td>2.36±0**</td>
<td>1±0.40*</td>
<td>9.88±0.29*</td>
<td>1.05±0.04**</td>
<td>0.099±0.006</td>
</tr>
</tbody>
</table>

**P <0.0001, **P <0.01, *P <0.05. RCRE: *Ricinus communis* root extract, 5-ASA: 5- Aminosalicylic acid, *R. communis: Ricinus communis*

**Figure 4:** Photomicrographs of sections of colons from rats of various groups stained with H and E. Colon microscopic image: (a) Normal rat with normal mucosal morphology, (b) dextran sodium sulfate induced colitis rats with extensive mucosal damage and inflammation, (c) 5- Aminosalicylic acid (500 mg/kg) treated rats with mild mucosal damage and inflammation, (d) *Ricinus communis* root extract (RCRE) (250 mg/kg) treated rats with mucosal damage and inflammation, and (e) RCRE (500 mg/kg) treated rats with mild mucosal damage and inflammation

(P < 0.0001) prevented the increase in MPO and NO level as compared to model control rats.

Furthermore, pre-treatment with 5-ASA and RCRE (250 and 500 mg/kg) prevent an increase in MDA level as compared to model control rats. However, the difference was not found to be statistically significant.

Treatment with DSS significantly decreased (P < 0.01) SOD activity in model control rats, which was significantly (P < 0.01) increased by pre-treatment with 5-ASA (500 mg/kg) and RCRE (500 mg/kg). However, the results with RCRE (250 mg/kg) were not found to be statistically significant [Table 2].

**DISCUSSION**

UC is a chronic, idiopathic, and relapsing disease that causes inflammation and ulceration of colonic mucosa. Its etiology remains undetermined but results from many studies suggest that it is related to an abnormal immune response in the gastrointestinal tract possibly associated with genetic and environmental factors. Pathological findings associated with UC are increased in certain inflammatory mediators, including cytokines, nitrogen and oxygen-derived free radicals, signs of oxidative stress, deranged colonic milieu, and increase in intestinal permeability.[2,3]

In this investigation, the protective effect of RCRE was evaluated against DSS-induced colitis in rats. DSS induced colitis is a reproducible model that morphologically and symptomatically resembles UC in humans.[29,30] Some researchers have reported that the use of 2-5% DSS (w/v) (50,000 Da) in drinking water for a period of 5-9 successive days induces colitis in Sprague-Dawley or Wistar rats.[20-22,26] It induces colitis by causing erosion with complete loss of surface epithelium. It causes deformity in the epithelial integrity, thereby increasing colonic mucosal permeability.[20,22,23] DSS-induced colitis causes morphological, histological and macroscopical changes characterized by hyperemia, ulcerations, moderate to severe submucosal edema, lesions, infiltration of granulocytes, and soft stool along with hemoccult.[21,14] DSS also significantly increases the production of all pro-inflammatory cytokines in both mid and distal colon.[13]

RCRE treatment results in improvement of DSS-induced colitis in rats by ameliorating stool consistency and improving body weight when compared to DSS-treated model control rats.

In this study UC-induced by DSS was associated with inflammation along with macroscopic, microscopic, and biochemical changes. By virtue of its healing property, administration of RCRE improved the histological score by ameliorating the disruption of colonic architecture. It also improved macroscopical score as evidenced by attenuation of mucosal damage and wall thickening as compared to DSS control rats.

Increase in weight and length of colon along with elevated weight/length ratio produced by DSS reflect the degree of local inflammation, edema, and wall thickening. The weight of the colon tissue is elevated due to an inflammatory response which is indicative of severity and extent of the disease.[36] All these parameters are significantly decreased by RCRE, suggesting its anti-inflammatory activity.

Several experimental studies have demonstrated that increased infiltration of leukocytes into the colonic mucosa contributes...
Table 2: Effect of RCRE (250 and 500 mg/kg) and 5-ASA (500 mg/kg) on colonic oxidative parameters such as, myeloperoxidase content, malondialdehyde level, nitric oxide level, and superoxide dismutase activity

<table>
<thead>
<tr>
<th>Groups</th>
<th>MPO (U/mg protein)</th>
<th>MDA (nM/g protein)</th>
<th>NO (nM/mg protein)</th>
<th>SOD (U/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>10.74±4.40</td>
<td>0.96±0.39</td>
<td>1.27±0.56</td>
<td>100±40.98</td>
</tr>
<tr>
<td>Model control</td>
<td>47.20±19.34**</td>
<td>4.45±1.82</td>
<td>2.68±1.20**</td>
<td>39.03±5.99*</td>
</tr>
<tr>
<td>5-ASA (500 mg/kg)</td>
<td>12.08±4.95**</td>
<td>2.02±0.83</td>
<td>1.79±0.80**</td>
<td>92.69±37.98#</td>
</tr>
<tr>
<td>RCRE (250 mg/kg)</td>
<td>21.21±8.69**</td>
<td>3.81±1.56</td>
<td>2.47±1.10**</td>
<td>43.91±17.99</td>
</tr>
<tr>
<td>RCRE (500 mg/kg)</td>
<td>13.94±5.71**</td>
<td>3.49±1.43</td>
<td>2.07±0.92**</td>
<td>85.37±34.98#</td>
</tr>
</tbody>
</table>

**P<0.0001, *P<0.01, RCRE: Ricinus communis root extract, 5-ASA: 5- Aminosalicylic acid, MPO: Myeloperoxidase, MDA: Malondialdehyde, R. communis: Ricinus communis, SOD: Superoxide dismutase, NO: Nitric oxide

significantly to the tissue necrosis and mucosal dysfunction, as they represent a major source of reactive oxygen species (ROS) including superoxide, hydrogen peroxide, and hypochlorous acid, which induce oxidative stress. ROS attack the cellular macromolecules, thus disrupting epithelial integrity and hindering mucosal recovery, especially in the case of impaired endogenous defense systems. Excessive generation of ROS leads to various pathological processes such as inflammation.

MPO is a good marker of neutrophil infiltration, inflammation and tissue injury. Elevated level of MPO in colonic tissue resulted in the production of superoxide anion, which contributed to the tissue necrosis and mucosal dysfunction in DSS control rats. RCRe significantly attenuated this elevated level of MPO by virtue of its antioxidant property.

Increased level of MDA as a marker of lipid peroxidation in association with higher MPO activity confirms the role of free radicals in DSS-induced colitis. Reduction in MDA level in RCRE treated rats shows its protective effect against DSS-induced colitis.

Colonic nitrite level serves as a sensitive marker of disease activity and toxicity in colitis. NO is an unconventional intracellular messenger, playing a key role in various pathological and physiological processes. It interacts with ROS, resulting in cellular damage. Pre-treatment with RCRE restores the elevated level of colonic NO and protects colonic mucosa from damage.

SOD plays an important role in protecting cells from oxidative damage by converting superoxide (O2-) into H2O2. In the case of SOD deficiency or increased superoxide production, O2- reacts with NO to produce RNS, such as peroxynitrite (ONOO-), which can cause oxidative/nitrosative stress. Several studies have reported that administration of SOD suppresses DSS and TNBS induced colitis by decreasing ROS level in the colon. Our results are in correlation with these studies, indicating RCRE suppresses the DSS-induced colitis through enhancement of antioxidant functions in the colon.

Wide ranges of phytoconstituents are responsible for the anti-inflammatory and antioxidant activity including phenolic compounds, alkaloids, tannins, and saponins. Several mechanisms have been proposed to explain the anti-inflammatory action of phytoconstituents: (i) Antioxidative and free radical scavenging activities, (ii) modulation of cellular activities of inflammation related to cells, (iii) modulation of pro-inflammatory enzyme activities, and (iv) modulation of pro-inflammatory gene expression. Phytochemical screening of the RCRE revealed the presence of carbohydrate, glycosides, saponins, flavonoids, alkaloids, tannins, and phenolic compounds. These phytoconstituents have been found to be effective in various models of IBD and may explain the antioxidant and anti-inflammatory activity of RCRE.

CONCLUSION

From the results of our experiments, we conclude that RCRE in the dose of 500 mg/kg exerts a protective effect against DSS-induced UC in Sprague-Dawley rats by its anti-inflammatory and free radical scavenging or antioxidant activity more or less comparable to standard drug 5-ASA (500 mg/kg). This lends pharmacological support to folkloric, ethnomedical uses of this plant in the management of UC, which is an inflammatory disease of the colon with oxidative stress as the main etiology.

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