Sulfated-polysaccharide fraction extracted from red algae *Gracilaria birdiae* ameliorates trinitrobenzenesulfonic acid-induced colitis in rats


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**Keywords**
antioxidant; colitis; *Gracilaria birdiae*; sulfated polysaccharide; TNBS

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Received December 4, 2013
Accepted January 18, 2014
doi: 10.1111/jphp.12231

**Abstract**

**Objectives** The aim of this study was to evaluate the protective effect of the sulfated-polysaccharide (PLS) fraction extracted from the seaweed *Gracilaria birdiae* in rats with trinitrobenzenesulfonic acid (TNBS)-induced colitis.

**Methods** In the experiments involving TNBS-induced colitis, rats were pretreated with polysaccharide extracted from *G. birdiae* (PLS: 30, 60 and 90 mg/kg, 500 μL p.o.) or dexamethasone (control group: 1 mg/kg) once daily for 3 days starting before TNBS instillation (day 1). The rats were killed on the third day, the portion of distal colon was excised and washed with 0.9% saline and pinned onto a wax block for the evaluation of macroscopic scores. Samples of the intestinal tissue were used for histological evaluation and assays for glutathione (GSH) levels, malonyldialdehyde (MDA) concentration, myeloperoxidase (MPO) activity, nitrate and nitrite (NO₃/NO₂) concentration and cytokines levels.

**Key findings** PLS treatment reduced the macroscopic and microscopic TNBS-induced intestinal damage. Additionally, it avoided the consumption of GSH, decreased pro-inflammatory cytokine levels, MDA and NO₃/NO₂ concentrations and diminished the MPO activity.

**Conclusions** Our results suggest that the PLS fraction has a protective effect against intestinal damage through mechanisms that involve the inhibition of inflammatory cell infiltration, cytokine releasing and lipid peroxidation.

**Introduction**

The study for natural products with pharmacological properties has significantly contributed to the discovery of compounds with important applications.[1,2] Recently, marine algae have attention as a source of bioactive substances for the development of new drugs.[3] In particular, algae are a very important and commercially valuable resource for the food industry; they also serve as soil conditioners and are used in traditional folk medicine due to their known health benefits.[4,5]

Red seaweeds produce an innumerous variety of sulfated galactans and are rich sources of sulfated polysaccharides (PLS). PLS from the *Gracilaria* genus are composed mainly of the alternating 3-linked-β-D-galactopyranose unit (Gal) and the 4-linked-3,6-anhydro-α-L-galactopyranose unit (AnGal). The Gal unit can be substituted for either methyl or sulfate ester radicals.[6]

Recent studies have shown that PLSs extracted from marine red algae demonstrated antioxidant and anti-inflammatory effects,[7,8] decreasing the production and releasing of free-radical scavengers and preventing oxidative damage in the living organism.[9] However, few studies have correlated the protective effect of PLSs from seaweeds to the intestinal damages associated with the colitis induced by trinitrobenzenesulfonic acid (TNBS).
The inflammatory bowel diseases (IBD) refer essentially to two different diseases: Crohn’s disease and ulcerative colitis (UC). Although the aetiology of IBD remains unclear, there is evidence that it involves immune, genetic and environmental factors, which are related to the initiation and development of colitis.[10,11] In the IBD, there is an increasing number of inflammatory cells that are found in areas of the intestine with chronic inflammation, resulting in overproduction of a variety of pro-inflammatory mediators including eicosanoids, platelet-activating factor, releasing of pro-inflammatory cytokines and specimens reactive of oxygen and nitrogen metabolites.[10–13]

Currently, there is no effective therapy to cure the disease but the mainstream treatment depends on reduction of the abnormal inflammation in the colon lining, and thereby relieves the symptoms of disease. The treatment depends on the severity of the disease; therefore treatment is adjusted for each individual.[14] Most people with mild or moderate IBD are treated with corticosteroids to reduce inflammation and relieve symptoms.[15] Nearly 25% of patients with UC requiring steroids therapy become steroid dependent after 1 year, and virtually all develop steroid-related adverse events.[16]

Considering the data above, it is plausible that the red algae and their derivative, the PLS, demonstrated marked antioxidant and anti-inflammatory effect, decreasing the production of free-radical scavengers and preventing oxidative damage. Thus, this study aimed at evaluating the protective effect of PLS fraction extracted from red algae G. birdiae in the trinitrobenzenesulfonic acid (TNBS)-induced colitis in rats.

Methods

Extraction of the PLS fraction

The extraction of the polysaccharide of G. birdiae was accomplished at the Laboratory of Biochemistry of Sea Algae at the Department of Biochemistry and Molecular Biology of the Federal University of Ceará. The marine red algae Gracilaria was collected at Flecheiras beach, Trairi, Ceará, Brazil, in September 2006, geographical localization: 03°13′ 25′′ S and 39°16′ 65′′ W. A voucher specimen (No. 40781) was deposited in the Herbarium Prisco Bezerra in the Department of Biological Sciences, Federal University of Ceará, Brazil. The samples were cleaned of epiphytes, washed with distilled water and stored at −20°C. The extraction procedure of polysaccharide was performed according with method previously described.[17]

Chemical structure of PLS fraction

The chemical structure was previously described.[18,19] Total sugar content of each fraction was determined according to the method of Dubois.[20] Protein fractions were obtained by Bradford’s method.[21] Sulfate content was determined by the barium chloride gelatine method,[22] and the monosaccharide contents of red seaweed galactans was obtained by reductive hydrolysis.[23]

Animals

Male Wistar rats (160–180 g) deriving from Federal University of Piauí (UFPI). The animals were housed at 25 ± 2°C under a 12/12 h light/dark cycle and were deprived of food for 12–16 h before the experiments, with free access to water. Experiments were conducted in accordance with current established principles for the care and use of research animals (National Institutes of Health guidelines) and were approved by Ethics Committee of the Federal University of Piauí (protocol nº 036/12).

Induction of colitis

Colitis was induced (n = 6 rats/group) by intracolonic single instillation of a solution of 20 mg of TNBS in 50% ethanol (EtOH), and the animals were previously anesthetized with ketamine (80 mg/kg; intramuscularly, i.m.) and xylazine (10 mg/kg, i.m.). Control groups received an equivalent volume of saline. A rubber catheter was inserted into the rectum, 8 cm distal to the anus, and the TNBS solution was introduced. Animals were placed head down in a vertical position for 30 s and then returned to their cages. Three days after the induction of colitis, the rats were killed and the experimental protocols executed as described below.

Treatment protocols

In the experiments involving TNBS-induced colitis, rats were treated with PLS (30, 60 and 90 mg/kg; orally, p.o.) or dexamethasone (1 mg/kg; subcutaneously, s.c.) once daily for 3 days before and after TNBS instillation (only on first day). On the third day after induction of TNBS-colitis, the rats were killed, and the abdomens were then opened, and after the identification of the intestine, the portion of distal colon was excised and washed with 0.9% saline. Then this segment, measuring 5 cm, was weighed to determine the colon oedema. The results were expressed in increase in colon weight (g)/5 cm ratios, compared with a normal control group, without colitis. The evaluation of macroscopic scores of lesion was performed by modifying the criteria previously described (Table 1).[24] Additionally, samples of intestinal tissue were then removed for the measurement of glutathione (GSH) concentration,[25] malondialdehyde (MDA) level,[26] myeloperoxidase (MPO) activity,[27] nitrate and nitrite (NO3/NO2) concentra-
tion\cite{28} and cytokine levels\cite{8} in inflamed colon tissue. Samples were fixed in 10% formalin for histopathological analysis.

**Histological evaluation**

For histological evaluation, the intestinal tissue was fixed in formalin for 24 h. After that, the samples were stored in a solution of 70% alcohol. The samples were embedded in paraffin and sectioned, and the sections were deparaffinized, stained with haematoxylin and eosin, and then examined under a microscope (blind analysis). The laminas were analysed according to the criteria described previously\cite{29}, in which scores are assigned to the following parameters: loss of mucosal architecture (score of 0–3), cellular infiltration (score of 0–3), muscle thickening (score of 0–3), crypt abscess (score of 0–1) and goblet cell depletion (score of 0–1).

**Myeloperoxidase assay**

This assay was performed to evaluate the neutrophil infiltration into the intestinal mucosa during TNBS-induced colon damage. Tissue samples were collected and homogenized (50–100 mg) in 50 mm 50 mm K2HPO4 buffer (pH 6.0) containing 13.72 mm hexadecyltrimethylammonium bromide. Then, homogenate was centrifuged (40 000 × g for 7 min at 4°C), and the supernatant assayed by spectrophotometry for MPO activity determination at 450 nm. The results were expressed as the MPO units per milligram of colon tissue\cite{27}.

**GSH levels**

The GSH levels in the fragments of intestinal tissue were determined according to the method described previously with modifications\cite{25}.

**MDA concentration**

The MDA concentration was measured using the method described previously with modifications\cite{26}.

**Measurement of nitric oxide (NO3/NO2) concentration**

Homogenate of intestinal tissue of the animals was incubated in a microplate with nitrate reductase for 12 h to convert nitrate (NO3) to nitrite (NO2). Nitric oxide production was determined by measuring nitrite concentrations in an ELISA plate reader at 540 nm using the Griess method\cite{28}. Results were expressed as micromoles of nitrite using the internal standard curve.

**Cytokine measurements**

Samples of intestinal tissue were collected and homogenized in sterile saline. After that, the interleukin IL-1β and tumour necrosis factor (TNF)-α levels were measured using ELISA kits according to the manufacturer’s recommendations\cite{8}. The homogenates were centrifuged at 0.8 g at 4°C for 10 min, and supernatants were stored at −80°C until further analysis. The results were expressed as picograms per millilitre of homogenate (pg/ml).

**Statistical analysis**

The results were expressed as means ± SEM. Statistical significance of differences between the groups was determined by one-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls test. For categorical variables, the Kruskal–Wallis test followed by Dunn’s test was performed. P < 0.05 was defined as statistically significant.

**Results**

**PLS structure**

The PLS fraction isolated from the red algae *G. birdiae* was previously identified\cite{15,16}. This galactan is an agar-type polysaccharide composed mainly by β-D-galactopyranose linked to 3,6-anhydro-α-L-galactose with low methyl substituted groups. The structure is formed by →4–3,6 anhydro-α-L-galp (1→3) β-D-galp 1→ segments, with the possibility of an α-L-galp unit substituted at the 6-position for a sulfate ester\cite{16}. In addition, the molar mass distribution was found to be within 2.6 × 10^6 and 3.75 × 10^5 g/mol, while the soluble carbohydrate, protein and sulfate contents were 85.5%, 2.5% and 8.4%, respectively\cite{15,16}.

**PLS reduced TNBS-induced macroscopic lesion scores**

In Figure 1, we can observe that the administration intracolon of TNBS induced a significant (P < 0.05) increase of colon macroscopic intestinal lesions (18.00 ± 2.2 scores of lesion) when compared with saline group (0.60 ± 0.04 scores of lesion). The treatment with PLS (30,
60 and 90 mg/kg, p.o.) reduced (30 mg/kg: 4.40 ± 1.03 scores of lesion; 60 mg/kg: 3.20 ± 1.02 scores of lesion; 90 mg/kg: 2.80 ± 0.42 scores of lesion) the damage scores of macroscopic lesions in the colon tissue, with the maximal effect observed at a dose of 90 mg/kg. Similar effects were produced by dexamethasone (5.50 ± 1.65 scores of lesion) administration, a drug of choice for treating IBD.

**Histopathological evaluation**

TNBS-induced colitis promotes change in histological findings characterized by severe intestinal damage, a massive inflammatory cell infiltration, ulceration and muscle thickening. The histological examination of colon sections from those rats that received only TNBS into the colon revealed the presence of crypts showing extensive epithelial destruction (Figure 2 and Table 2). The histological evaluation of colons from rats treated with PLS 90 mg/kg revealed a pronounced reduction in the inflammatory response with moderate loss of epithelial cells and minimal inflammatory infiltration into the colonic tissue, resulting in a decreased microscopic damage score and showing a reduction of 45% in the total damage score, as compared with TNBS group.

**PLS reduced TNBS-induced increase in wet weight of the colon**

In Figure 3, we observed that TNBS induced a significant ($P < 0.05$) increase in the colon weight (1.03 ± 0.03 g; 75%) of the injured area in 5 cm of the bowel tissue, as compared with saline group (0.26 ± 0.01 g) or Dexa Group (0.68 ± 0.05). However, pretreatment with PLS 90 mg/kg significantly reversed (0.55 ± 0.05 g) the colon injury after TNBS colonic instillation.

**PLS reduced TNBS-induced MPO activity**

Figure 4 shows that the TNBS into the colon determined MPO activity in the concentration of 11.78 ± 2.393 units of MPO/mg of colon tissue, while the group treated with PLS 90 mg/kg decreased an activity of this enzyme at 2.578 ± 1.415 UMPO/mg of colon tissue, which was equivalent to a reduction of 78%.

**PLS treatment interferes with TNBS-induced GSH and MDA levels in rat intestine**

As showed in Figure 5A, the colitis produced a significant ($P < 0.05$) decrease in colonic GSH content (91.56 ± 14.96 mg/g of tissue) as compared with the saline group.
The treatment for 3 days with PLS in dose of 90 mg/kg prevents the consumption of GSH (286.30 ± 57.07 mg/g of tissue), which remained at a much higher concentration as compared with TNBS control group. On the other hand, Figure 5B shows that the oxidative stress in colonic mucosa induced by TNBS was evidenced by the significant increased of MDA (162.5 ± 25.63 nmol/g of tissue) concentration when compared with saline group (65.07 ± 17.93 nmol/g of tissue). PLS 90 mg/kg was able to inhibit the increase of MDA (23.95 ± 4.72 nmol/g of tissue) levels in inflamed mucosa tissue.

**Nitric oxide (NO3/NO2) concentration**

As shown in Figure 6, the TNBS group showed an increased level of NO3/NO2 in colon tissue (0.23 ± 0.03 μm) when this group was compared with saline group (0.08 ± 0.01 μm). The treatment of PLS reduces the levels of nitrate and nitrite to (0.08 ± 0.00 μm) in the intestinal damage caused by TNBS instillation into the colon.

**PLS decreased TNBS-induced IL-1β and TNF-α production**

Figure 7 shows that the intracolonic administration of TNBS induced an increased of IL-1β (panel A; 6630 ± 561.5 pg/ml) and TNF-α (panel B; 106.8 ± 19.97 pg/ml) levels, comparing this group with saline group (IL-1β: 187.4 ± 31.65 pg/ml; TNF-α: 26.99 ± 7.771 pg/ml). Moreover, the treatment with PLS 90 mg/kg significantly reduced the concentrations of these cytokines (IL-1β: 2872.00 ± 267.20 pg/ml; TNF-α: 26.99 ± 2.67 pg/ml).

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<td>Loss mucosal architecture</td>
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PLS, polysaccharide; TNBS, trinitrobenzenesulfonic acid. Score for histological damage expressed as mean ± SEM (n = 5). *P < 0.05 versus saline group; #P < 0.05 versus TNBS group (Kruskal–Wallis non-parametric test and Dunn’s test were used for multiple comparisons of histological analyses).
Discussion

The inflammatory bowel diseases (IBD) refer essentially to two different, yet closely related conditions: Crohn’s disease and UC.[30] The development of inflammatory bowel disease (IBD) is characterized by frequent episodes of diarrhoea, abdominal pain, blood in the stool and weight loss over a period of months to years.[31] This leads to a discomfort and low quality of life for the person who bears this disease.

IBD is related to an abnormally exacerbated immune system to otherwise innocuous stimuli which are not properly abrogated by the feedback system normally downregulating the mucosal response towards luminal factors.[31] Early events of IBD occur long before symptoms appear. Thus, study in humans often needs to be retrospective, what can cause many errors. That has led to studies of animal models of IBD to determine early events in the disease process and to test new treatments.[32,33]

In this context, TNBS is a substance used as a valuable model to investigate the pathophysiological mechanism of IBD. Histological modifications occur in TNBS-induced colitis resemble that of IBD in terms of ulceration, inflammation and leucocyte infiltration. Although the acid property of TNBS is partly responsible for the mucosal damage, TNBS has been shown to elicit intestinal protein antigenicity by functioning as a hapten,[34] thereby developing an immune and inflammatory responses. The early acute phase of TNBS-induced inflammation is presumably essential to establish the continued progression of the colitis that is mediated by the T-cell dependent immunity.[35]

Many marine algae and their isolated constituents have shown beneficial therapeutic properties including analgesic, anti-inflammatory and gastroprotective actions.[30,36,37] Knowing that marine algae are an important therapeutic tool against gastrointestinal injury, this study aims to verify the effect of PLS fraction extracted from G. birdiae in TNBS-induced colitis in rats.

The results of this study demonstrated, for the first time, the effectiveness of the PLS action extracted from G. birdiae against TNBS-induced large intestine damage on the macroscopic and histological examinations in rats. These parameters were used as an indicator of disease-associated intestinal wall thickening and intensity of inflammation.[38] According to our results, we can infer that PLS fraction produce anti-inflammatory effect in TNBS-induced colon damage in rats.

Another parameter studied was the wet weight of the colon in animals with or without colitis. Our results demonstrated that the PLS 90 mg/kg decreased the wet weight of the colon. TNBS-induced colitis resembles that of IBD in terms of ulceration, inflammation and leucocyte infiltration,[39] causing an intense injury leading to an increase in

![Figure 5](image1.png)

**Figure 5** Effect of the PLS fraction extracted from *Gracilaria birdiae* on glutathione levels (a) and MDA concentration (b) in TNBS-induced colitis. Animals were treated with saline (sal: control), PLS (90 mg/kg p.o.) once daily for 3 days. On the third day, the rats were killed, the samples of colon were harvest, and glutathione level was evaluated. The results are expressed as the mean ± SEM of 5–7 animals per group. *P < 0.05 versus TNBS group; *P < 0.05 versus saline group (ANOVA followed by the Newman–Keuls post-hoc test).

![Figure 6](image2.png)

**Figure 6** Effect of the polysaccharide fraction extracted from *Gracilaria birdiae* on intestinal tissue concentration of nitric oxide (NO3/NO2). In the assay, animals were treated with saline (sal: control), PLS (90 mg/kg, p.o.) once daily for 3 days. On the third day, the rats were killed, the samples of colon were collected, and NO3/NO2 concentration was measured. The results are expressed as the mean ± SEM of 5–7 animals per group. *P < 0.05 versus TNBS group; *P < 0.05 versus saline group (ANOVA followed by the Newman–Keuls post hoc test).
volume and weight of damaged intestine. Corroborating to the previous results, our substance decreased the inflammatory process in the colonic mucosa.

We can observe in our results the improvement of microscopic scores of lesion in the treatment with PLS (90 mg/kg). This substance also decreases the inflammatory response resulting and minimal inflammatory infiltration into the colonic tissue. Neutrophils were attributed as the cells responsible for disrupting epithelial integrity and causing colon injury in IBD. Thus, the reduction of neutrophil infiltration in the animals treated with PLS contributes to the reduction in neutrophil-mediated colon tissue injury during colitis.

Corroborating with our results above, PLS fraction also decreased MPO activity. Neutrophil infiltration into the lamina propria is a common feature of colitis and probably accounts for significant non-specific injury from this disease. During the migration, the neutrophils released MPO to penetrate into the injury tissue. MPO is an enzyme mainly found in azurophilic granules of neutrophils that produce the microbial molecule hypochlorite, a strong oxidant, upon the reaction with H₂O₂ and Cl⁻. Moreover, it can serve as a good marker of inflammation, tissue injury and neutrophil infiltration in gastrointestinal tissues. Thus, we can infer that the PLS decrease the mucosal damage by decreasing free radicals production derived of neutrophil infiltration during the inflammation in the colon.

Oxidative stress has been proposed to play an important role in the pathogenesis of inflammatory bowel disease and is related to neutrophil infiltration within the inflamed colon mucosa. The recruitment and activation of neutrophils during acute inflammation contribute to the overproduction of reactive oxygen and nitrogen species that overwhelm the tissue antioxidant protective mechanisms, resulting in oxidative stress, which perpetuates inflammation of the colon. Therefore, this study investigated three oxidative stress markers: GSH and MDA and NO₃/NO₂ concentration.

Antioxidant compounds play an important role in various pathological conditions, including inflammation, neurodegenerative diseases and cancer. It has been systematically reported in the literature that PLSs showing antioxidant activity, such as those extracted from marine algae, protect against cell death due to their ability to degrade excessive reactive oxygen species. Nevertheless, few studies have correlated antioxidant potential with TNBS-associated injury of the intestinal tissue.

Our results demonstrated that the PLS fraction increased the levels of GSH in animals with TNBS-induced colitis. GSH, an endogenous antioxidant, protects the cells against oxidative damage, keeping the sulfhydryl groups (–SH) of proteins reduced and preventing them from reacting with free radicals. Concentrations of endogenous antioxidants, such as GSH, are decreased significantly in patients with inflammatory bowel disease and in experimental models of colitis. According this result, we can infer that PLS decreased the mucosa damage acting in the production and action of endogenous antioxidants.

Oxidative damage in colon tissue is a potential aetiopathological or triggering factor for IBD, because the detrimental effects of reactive oxygen molecules have been well established in the inflammation process. MDA is a product of liperoxidative processes that take place as a consequence of the colonic oxidative insult. Our results demonstrated for the first time that the PLS reduced the MDA concentration in the colonic inflamed mucosa. Thus, we can infer that the action of PLS to reduce the inflammatory response in the colon is seemingly related to the decrease of oxidative stress.

The damage in intestinal mucosa induced by TNBS was accompanied with high levels of free radicals derivate of the degradation of NO (NO₃/NO₂ radicals). Our result demonstrated that the PLS treatment decreased the
concentration of NO/NO2 in the intestinal mucosa of the rats treated with TNBS. NO is a free radical with moderate reactivity. Its production in large quantities via the upregulation of inducible nitric oxide synthase (iNOS) can inhibit key enzymes in the mitochondrial electron transport chain. In addition to this, high levels of nitric oxide from activated iNOS are toxic and can damage the tissue directly by the peroxynitrite formation after reaction with superoxide. Thus, we infer the PLS has protective action against intestinal injury by decreasing the formation of peroxynitrite.

The inflammatory cells infiltration in the colitis is dependent of the overproduction of several pro-inflammatory mediators, for example cytokines. Our results demonstrated that PLS 90 mg/kg decreased the concentration of these cytokines in inflamed intestinal mucosa. Cytokines, such as IL-1β and TNF-α, are increased in inflamed tissue, including the mucosa of IBD lesions. These mediators are responsible for many of the features of inflammation; an important feature of UC is the recruitment of neutrophils and mononuclear cells. Leucocyte adherence and recruitment are increased in the micro-vessels in chronic disease, mediated in part by the upregulation of adhesion molecules towards vascular endothelial cells by TNF-α and IL-1β. Moreover, increased levels of tissue-specific and inflammatory chemokines enhance leucocyte migration. Thus, these results revealed that the PLS has an action to reduce the inflammatory response through inhibition of pro-inflammatory cytokines in the intestine injury resulted from TNBS-induced colitis in rats. A possible mechanism may involve the downregulation of the inflammatory response by inhibiting the synthesis and release of pro-inflammatory mediators.

Conclusions

In conclusion, our results suggest that PLS has a protective effect in the TNBS-induced colitis in rats, through mechanisms that involve the inhibition of inflammatory cell infiltration, reduction in the oxidative stress and of pro-inflammatory cytokines concentration. Thus, we suggest that PLSs may have potential applications in the development of novel therapeutic targets against the inflammatory bowel disease in humans.

Acknowledgements

The authors are grateful to the Brazilian Agency for Scientific and Technological Development-CNPq (Brazil) and the technical assistance of Maria Silvandira Freire França.

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