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Diet containing seeds of *Buchholzia coriacea* accelerates healing of acetic acid induced colitis in rats

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ABSTRACT

Objective: To investigate the anti-colitic effects of diet containing seeds of *Buchholzia coriacea* (*B. coriacea*) on acetic acid induced ulcerative colitis. **Methods:** Male Wistar rats (70-100 g) were fed with standard diets (control group) or with same diet containing *B. coriacea* seeds at 12.5% or 25% for six weeks. At the sixth week, colitis was induced by intra-rectal administration of 1 mL/200 g 6% acetic acid. Animals were sacrificed at days 0 (before induction), 1, 3 and 7 post induction to assess disease severity via evaluation of stool consistency, haematological variables and histomorphometry of colon tissues. **Results:** A significant increase in body weight was observed in the 12.5% *B. coriacea* fed group compared to the control. *B. coriacea* significantly reduced stool consistency and microscopic scores. Histological evaluation revealed significantly decreased inflammatory aggregates in *B. coriacea* fed groups compared to control after colitis induction. There was a significant decrease in packed cell volume, red blood cell and haemoglobin concentration in the control group at day 1 post colitis induction compared to 12.5% *B. coriacea* fed groups. Neutrophils and white blood cell were also significantly increased after colitis induction in the control group while these were significantly decreased in the *B. coriacea* fed groups. **Conclusions:** The addition of *B. coriacea* seeds to diets promotes healing of acetic acid induced colitis by suppressing infiltration of inflammatory aggregates and ameliorating anemia.

1. Introduction

Inflammatory bowel disease is an umbrella term used to describe ulcerative colitis and Crohn's disease. It is characterized by superficial infiltration of the bowel wall by inflammatory white blood cells, resulting in multiple mucosal ulceration and crypt abscesses[1]. Ulcerative colitis is a disease usually associated with

the western developed countries such as United Kingdom, United States and Canada[2,3], however, in recent times, cases of the disease are now being diagnosed in developing countries such as China[4], Nigeria[5] and this may be due to civilization and industrialization spreading across the world at a very fast rate.

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The typical symptom of ulcerative colitis is diarrhoea which is usually associated with bloody stool. Bowel movements are frequent but small in volume as a result of rectal inflammation[6]. Other symptoms include fever and pain, which may be in either the lower quadrant or rectum. Systemic features, including fever, malaise, and weight loss are more common if a greater portion of the colon is affected[6]. Ulcerative colitis is an intermittent disease, with periods of exacerbated symptoms and periods that are relatively symptom-free. Symptoms sometimes however can diminish on their own but usually require treatment to go into remission[7].

Ulcerative colitis has been known as a clinical entity as early as 1859, however, the aetiological mystery is yet to be completely unraveled[8]. Various factors have been reported to be involved in the disease formation condition which include an increase in reactive oxygen species leading to oxidative stress[9,10] and in pro-inflammatory cytokines such as IL-8, IL1 β and TNF- α [11,12] as well as genetic and environmental factors[13].

Until recently, the clinical treatments for ulcerative colitis were relatively limited, essentially comprising of 5-aminosalicylic acid (ASA) compounds, steroids and azathioprine/ 6-mercaptopurine. In the 1990s, methotrexate and cyclosporine were included as immunoregulatory agents used in inflammatory bowel diseases. The approval of infliximab (Remicade; Centocor), a chimeric monoclonal antibody which targets tumor-necrosis factor- α , for the treatment of ulcerative colitis disease launched the era of biologic therapy for inflammatory bowel diseases[14]. These varieties of medications used in treatment of ulcerative colitis fall into two categories; maintenance drugs which are taken all the time to prevent flare-ups and fast-acting drugs which are taken occasionally to stop a flare up[15]. Many people who have ulcerative colitis turn to alternate therapies in addition to medical management of their disease[16]. This alternative therapy includes natural plant products and the use of plant extracts for the disease treatment. Some of the herbs and supplements that have been studied include *Aloe vera*, *Boswellia*, butyrate, licorice root, slippery elm, and omega-3 fatty acids. Some of these remedies have shown promise for ulcerative colitis but others have not been shown to have any value, and may actually be harmful[16].

Buchholzia coriacea (*B. coriacea*) is a forest tree belonging to the Capparaceae family[17]. It was named after R. W. Buchholz who collected plants in Cameroon in the late 19th century[18]. The seeds of the plant are edible, taste peppery and are known to have great medicinal value which gave the plant its common name ‘wonderful kola’[19]. Over the years, the plant has been used in different parts of African countries to treat various illnesses ranging from headache, nasal congestion, small pox, cough, fever and also used as an antihelmintic agent[20–22].

Recent studies on the seed extract of this plant have shown that it is a good source of energy[19]; it possesses antibacterial, anti-diabetic,

hypolipidemic, antioxidant and anti-ulcer activities[23–25]. Despite the various reports on the plant use to treat various illnesses, information on the use of the seeds of the plant in gastrointestinal ulceration is scarce. However, there is no report on its effect on ulcerative colitis, thus the present study was undertaken to evaluate the effect of diet containing seeds of *B. coriacea* on healing experimentally induced ulcerative colitis.

2. Materials and methods

2.1. Plant collection and preparation

The seeds of *B. coriacea* were purchased from Oje market in Ibadan, Oyo State. The seeds were washed, peeled, air dried and thereafter milled into powdery form. It was then incorporated into the feed of the animals at varying percentages.

2.2. Experimental design

The animals used in this study were male Wistar rats obtained from the central animal house, University of Ibadan. All protocols in this study were approved by the Gastrointestinal Research Group of the University of Ibadan, Ibadan, Nigeria and carried out in accordance with the guidelines of the National Institute of Health for laboratory animal care and use.

A total of 60 rats weighing between 70-100 g were used and divided into three groups of 20 rats each. Animals were fed with standard rat diet for the control group, and with same diet containing 12.5% *B. coriacea* and 25% *B. coriacea* for six weeks and all groups received water *ad libitum*. At the end of six weeks, 15 animals were randomly selected from each group for the induction of colitis and thereafter continued with same diet for the period of assessment.

2.3. Induction of colitis

Under light ether anaesthesia, a flexible plastic catheter (outer diameter of 2 mm) was inserted rectally into the colon 8 cm proximal to the anus. Colitis was then induced by administering 1 mL/200 g 6% acetic acid[26]. The animals were inspected and scored for the presence of diarrhoea and 5 rats from each group were sacrificed at day 0 (without colitis), days 1, 3 and 7 after colitis induction.

2.4. Diarrhoea scoring

The stool consistency of each rat was assessed daily for diarrhoea and presence of blood using a standard scoring method[27] stated as follows.

- 0 - Normal stool (No traces of blood)
- 1 - Soft stool, but still formed
- 2 - Very soft + traces of blood
- 3 - Bloody diarrhoea.

2.5. Haematological analysis

Blood samples were collected from each animal at the days of sacrifice via cardiac puncture into ethylene-diamine-tetra-acetic acid bottle. Complete blood count analysis was carried out; packed cell volume (PCV), haemoglobin (Hb) concentration, red blood cell (RBC) count, platelets, white blood cell (WBC) count, lymphocytes and neutrophils[28].

2.6. Assessment of colon weight

After quick decapitation of the animals, the distal colon (8 cm) was removed and opened longitudinally, washed to remove luminal contents with ice cold normal saline. The colon was weighed with an electronic weighing balance, model DT 1000 with capacity of 0.01 to 100 g.

2.7. Histological observations

Small section of the 8 cm distal colon was taken from each colon and fixed in 10% formalin for histological examination. Each tissue was fixed, cut longitudinally into 5 mm sections, stained with Haematoxylin and Eosin (H&E). The slides were coded to prevent observer bias and evaluated blindly by light microscope. The extent of tissue injury was scored using the following criteria;

- 0 – No evidence of inflammation;
- 1- Low level of inflammation with scattered infiltrating mononuclear cells (1-2 foci);
- 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

2.8. Statistical analysis

All data were expressed as mean±SEM. Statistical comparison was performed across the groups using Graph Pad Prism6. Results were analyzed by Kruskal-Wallis test and Mann-Whitney for nonparametric variables while ANOVA and Student *t*-test were used for parametric variables. Significant differences were taken as *P*<0.05.

3. Results

3.1. Effect of *B. coriacea* on weekly body weight changes

The results on body weight showed feeding animals with diets containing *B. coriacea* had no adverse effect on body weight profiles as all the animals had increased body weight with weeks of treatment. However, the group fed with 12.5% *B. coriacea* gained weight at a significantly higher level from the second week compared with the other groups (Figure 1).

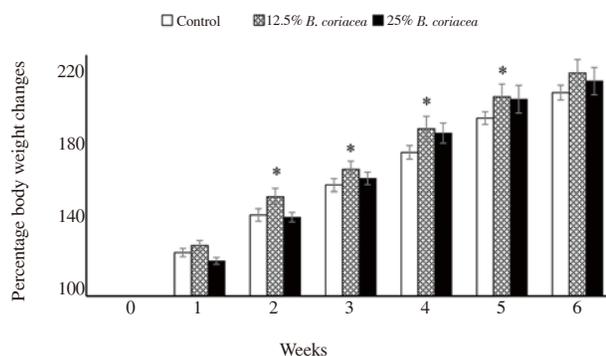


Figure 1. Effect of *B. coriacea* on weekly body weight changes.

Values are expressed as mean±SEM. **P*<0.05, compared to control group.

Table 1

Diarrhoea score and colon weight in control rats and those fed with diets containing 12.5% and 25% *B. coriacea* diet before and after acetic acid induced colonic injury.

Treatment	Diarrhoea score				Weight of 8 cm distal colon (g)			
	Pre-colitis	Day 1	Day 3	Day 7	Pre-colitis	Day 1	Day 3	Day 7
Control (0% <i>B. coriacea</i>)	0.00±0.00	0.40±0.16	1.73±0.24 (332.50%)	0.57±0.26 (42.50%)	0.30±0.04	1.023±0.04 (241.00%)	0.73±0.07 (143.30%)	0.83±0.03 (176.70%)
12.5% <i>B. coriacea</i>	0.00±0.00	0.67±0.19	0.92±0.26* (37.30%)	0.50±0.23 (25.30%)	0.38±0.02	0.68±0.05** (78.90%)	0.53±0.03* (39.50%)	0.52±0.04*** (36.80%)
25% <i>B. coriacea</i>	0.00±0.00	0.24±0.13	0.43±0.14** (79.20%)	0.70±0.21 (19.17%)	0.35±0.02	0.63±0.08** (80.00%)	0.44±0.03** (25.70%)	0.51±0.05*** (45.70%)

Values are expressed as mean±SEM.

Values in parentheses are percentages changes over Day 1 post colitis values for diarrhea scores or pre-colitis values for distal colon weight. **P*<0.05, ***P*<0.01, ****P*<0.001, compared to control group.

Table 2Effect of *B. coriacea* on RBC, PCV, Hb and platelet count.

	Groups	RBC ($\times 10^6/\mu\text{L}$)	PCV (%)	Hb (mg/L)	Platelet ($\times 10^5$)
Day 0	Control	6.49 \pm 0.91	40.50 \pm 1.43	12.87 \pm 0.53	1.57 \pm 0.14
	12.5% <i>B. coriacea</i>	6.77 \pm 0.09	38.00 \pm 2.19	14.40 \pm 0.14	1.56 \pm 0.14
	25% <i>B. coriacea</i>	6.03 \pm 0.48	35.50 \pm 2.01	11.53 \pm 0.73	1.89 \pm 0.06
Day 1	Control	4.44 \pm 0.22	29.00 \pm 1.64	9.30 \pm 0.67	2.00 \pm 0.19
	12.5% <i>B. coriacea</i>	6.74 \pm 0.40 [†]	42.00 \pm 1.34 ^{**}	13.97 \pm 0.54 ^{**}	1.50 \pm 0.19
	25% <i>B. coriacea</i>	4.78 \pm 0.65	33.25 \pm 2.78	10.37 \pm 1.09	1.88 \pm 0.10
Day 3	Control	5.34 \pm 0.78	31.00 \pm 1.07	10.37 \pm 1.83	1.95 \pm 0.11
	12.5% <i>B. coriacea</i>	6.00 \pm 0.39	36.70 \pm 2.23*	11.70 \pm 0.75	3.30 \pm 0.23 ^{**}
	25% <i>B. coriacea</i>	5.73 \pm 0.32	35.67 \pm 1.47 [†]	11.90 \pm 0.63	1.89 \pm 0.08
Day 7	Control	5.59 \pm 0.18	36.00 \pm 0.97	11.17 \pm 0.21	0.86 \pm 0.05
	12.5% <i>B. coriacea</i>	6.26 \pm 0.07 [†]	37.00 \pm 0.37	11.70 \pm 0.06	1.08 \pm 0.27 [†]
	25% <i>B. coriacea</i>	5.37 \pm 0.18	35.67 \pm 1.46	10.77 \pm 0.14	1.33 \pm 0.11 [*]

Values are expressed as mean \pm SEM. [†] P <0.05, ^{**} P <0.01, compared to control group.**Table 3**Effect of *B. coriacea* on WBC, neutrophils, lymphocytes and NLR.

	Groups	WBC ($\times 10^3$)	Neutrophils	Lymphocytes	NLR
Day 0	Control	7.87 \pm 0.72	33.67 \pm 0.91	64.33 \pm 1.28	0.53 \pm 0.02
	12.5% <i>B. coriacea</i>	7.82 \pm 0.50	30.33 \pm 0.70	66.00 \pm 0.63	0.46 \pm 0.01
	25% <i>B. coriacea</i>	9.25 \pm 0.28 [†]	35.50 \pm 1.11	59.00 \pm 1.78	0.58 \pm 0.04
Day 1	Control	11.32 \pm 0.60	39.67 \pm 0.56	58.33 \pm 0.21	0.68 \pm 0.01
	12.5% <i>B. coriacea</i>	8.49 \pm 0.54 [*]	29.67 \pm 0.56 ^{**}	65.33 \pm 0.21 [*]	0.45 \pm 0.01 ^{**}
	25% <i>B. coriacea</i>	9.34 \pm 0.51	33.00 \pm 2.39 ^{**}	62.67 \pm 2.48 [*]	0.54 \pm 0.06 ^{**}
Day 3	Control	9.73 \pm 0.53	30.67 \pm 0.76	66.00 \pm 1.10	0.47 \pm 0.02
	12.5% <i>B. coriacea</i>	7.25 \pm 0.83	29.00 \pm 1.83	66.67 \pm 2.21	0.44 \pm 0.04
	25% <i>B. coriacea</i>	9.45 \pm 0.42	28.67 \pm 0.56	67.67 \pm 0.43	0.42 \pm 0.01
Day 7	Control	4.90 \pm 0.19	26.33 \pm 2.31	70.00 \pm 3.48	0.38 \pm 0.01
	12.5% <i>B. coriacea</i>	7.75 \pm 0.13 ^{***}	25.67 \pm 2.43	70.67 \pm 3.66	0.35 \pm 0.05
	25% <i>B. coriacea</i>	8.82 \pm 0.19 ^{***}	16.00 \pm 1.46 ^{**}	81.00 \pm 0.73	0.20 \pm 0.02 ^{**}

Values are expressed as mean \pm SEM. [†] P <0.05, ^{**} P <0.01, ^{***} P <0.001, compared to control group.

3.2. Effect of *B. coriacea* on diarrhoea score and colon weight

The stools of animals in all groups were normal at day 0 before the induction of colitis, with diarrhoea score of 0.00 \pm 0.00. On induction of colitis, all groups showed signs of diarrhoea. As shown in Table 1, the diarrhoea score 24 h after inducing colitis was 0.40 \pm 0.16 in the control rats. The scores in the 12.5% and 25% *B. coriacea* diet groups were 0.67 \pm 0.19 and 0.24 \pm 0.13 respectively. Compared with the first day post-colitis, diarrhoea score in the control animals increased by 332.5%. Diarrhoea was however less frequent in the 12.5% *B. coriacea* (37.3%) and 25% *B. coriacea* (79.2%) fed rats. By day 7, the 12.5% *B. coriacea* diet had reduced diarrhoea score to levels below the 24-hour value (-25.3%), indicating that it had more significant anti-colitis effect.

Colon weight was also significantly reduced in the *B. coriacea* fed group in a dose dependent manner by days 1, 3 and 7 after colitis induction compared to the control group as shown in Table 1.

3.3. Effect of *B. coriacea* on hematological variables

Tables 2 and 3 summarized the effect of *B. coriacea* on hematological variables. It was deduced that there was no significant

difference in any of the parameters on day 0 prior to the induction of colitis. On induction of colitis, a significant decrease in PCV, RBC count and Hb concentration was observed in the control groups on days 1, 3 and 7. However, the 12.5% *B. coriacea* fed group had significantly higher PCV, RBC and Hb concentration compared to control group (Table 2). There was also a corresponding significant increase in WBC count, neutrophils count and neutrophil/lymphocyte ratio (NLR) in the control compared to *B. coriacea* groups on day 1 post colitis induction. On day 3, there was no significant difference in these variables between control group and *B. coriacea* fed groups, however, WBC was significantly higher in *B. coriacea* fed groups by day 7, while neutrophils and NLR were significantly increased in 25% *B. coriacea* group compared to control (Table 3).

3.4. Effect of *B. coriacea* on histological observation and score

There was no significant difference in the mean histological score between control group (0.00 \pm 0.00) and the *B. coriacea* fed groups; 12.5% (0.00 \pm 0.00) and 25% (0.25 \pm 0.25) on day 0 (pre-colitis). On induction of colitis, there was a marked increase in

the influx of inflammatory aggregates as well as severe ulceration and inflammation in control group, nevertheless, mild to moderate erosion and influx of inflammatory aggregates were observed in the *B. coriacea* fed groups (Figure 2) leading to a significant increase in the histological scores. On day 1 post colitis induction, there was no significant difference in histological scores between control group (1.25 ± 0.25) and *B. coriacea* fed groups; 12.5% (1.75 ± 0.25) and 25% (1.50 ± 0.29). Significantly low histological scores were recorded in the 12.5% *B. coriacea* group (1.60 ± 0.24 and 1.40 ± 0.24) and 25% *B. coriacea* group (2.20 ± 0.37 and 2.40 ± 0.24) on days 3 and 7 respectively compared to control group (3.00 ± 0.31 and 3.60 ± 0.24).

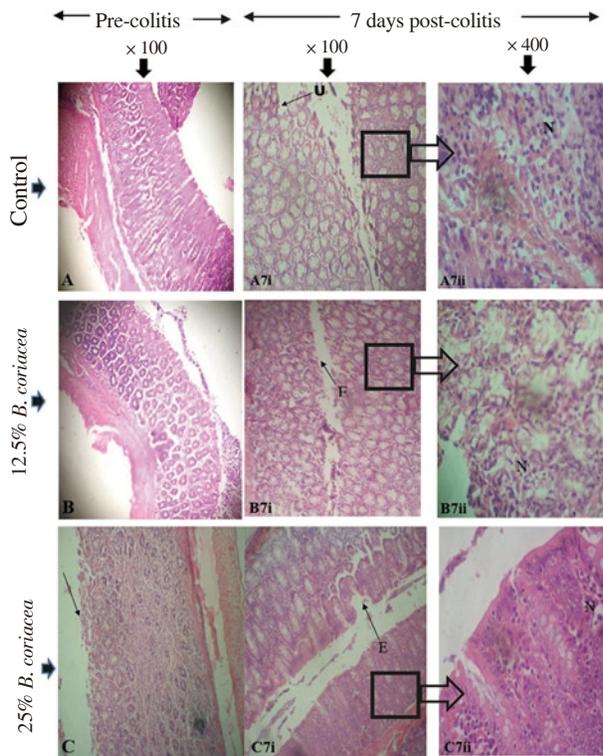


Figure 2. Photomicrograph collage of the colon of rats before (A, B, C) and after (A7, B7 and C7) acetic acid induced colitis.

A and B are control and 12.5% *B. coriacea* respectively showing intact epithelium. C represents 25% *B. coriacea* showing very mild erosion. A7i ($\times 100$) and A7ii ($\times 400$) show colon of control group (H&E) 7 d after colitis induction. U, ulceration and glandular degeneration. N, marked infiltration of inflammatory aggregates. B7i ($\times 100$) and B7ii ($\times 400$) show colon of 12.5% *B. coriacea* diet group 7 d after colitis induction. E, epithelial erosion. N, moderate infiltration of inflammatory aggregates. C7i ($\times 100$) and C7ii ($\times 400$) show colon of 25% *B. coriacea* diet group 7 d after colitis induction. E, moderate epithelial erosion and glandular degeneration. N, mild infiltration of inflammatory aggregates.

4. Discussion

The dietary life style of an individual is very paramount to determining the health condition of the person. Various disease conditions including ulcerative colitis have been associated with

poor dietary life style[29,30]. In this study, the incorporation of seeds of *B. coriacea* into the diets of rats had ameliorative effect on experimentally induced ulcerative colitis.

The result on weekly body weight changes showed that *B. coriacea* fed groups gained considerable weight more than the control group which was noticed two weeks after consumption of *B. coriacea*. This result is supported by the report of Amaechi[19], where the nutritive and anti-nutritive value of seeds of *B. coriacea* were evaluated. It was reported that the seeds contain high carbohydrate and protein content and low fat content, thus they can serve as a good source of energy as well as an alternative source of protein. Haematological observation from this study also indicated that the animals were healthy as there was no substantial difference between the *B. coriacea* fed groups (12.5% *B. coriacea* and 25% *B. coriacea*) and control group prior to the induction of ulcerative colitis.

The use of acetic acid for the production of ulcerative colitis in rats is a standardized model[10]. Acetic acid model of induction of ulcerative colitis has been reported to have similar histological features to that of human. It is usually associated with deep ulceration and inflammation, enhanced vasopermeability as well as severe influx of neutrophils and macrophages to the site of injury[31,32], hence, it is preferred in studying the healing potential of any proposed anti-colitic agent or drug. The influx of neutrophils and macrophages to the site of injury causes increase thickness of colonic wall with a resultant increase in colonic weight. In this study, the increased colon weight observed in the control group following the induction of colitis was decreased in the *B. coriacea* fed groups (12.5% *B. coriacea* and 25% *B. coriacea*). The apparent suppression of acetic acid induced colon weight by *B. coriacea* suggests its ability to prevent influx of neutrophils and macrophages to the site of injury. This result is buttressed by the histopathological observation, WBC and neutrophils count. Marked influx of inflammatory mediators into the submucosa layer was observed in the untreated group, while mild to moderate inflammatory mediators were observed in the submucosa layer in the *B. coriacea* fed groups. Likewise, the histological score further confirms these observations with the control group having a significantly increased histological scores compared to the *B. coriacea* fed groups.

Neutrophil recruitment is key in the onset and healing of ulcerative colitis. Neutrophil is a major source of reactive oxygen species, hence, plays a crucial role in the development of tissue damage[33]. Various studies have reported that activated neutrophils are capable of producing superoxide and a cascade of various species leading to a very reactive hydroxyl radical and peroxides[34,35]. Prolonged production of these reactive hydroxyl radicals and peroxides may overwhelm the endogenous antioxidant defense mechanism, leading to oxidative stress. Agents that can mop up reactive oxygen species, act as an exogenous antioxidants as well as boost the endogenous

antioxidants system, are likely beneficial in the treatment of chronic inflammatory disease. *B. coriacea* suppressed neutrophil infiltration noticed from histological observation as well as haematological parameters, hence can be proposed to have had a similar role in the level of free radicals. It has been reported[24] that methanol extract of *B. coriacea* significantly decreases serum malondialdehyde levels while increasing serum catalase and glutathione reductase activities in streptozotocin-induced diabetes.

Diarrhoea which is a major manifestation during ulcerative colitis leads to loss of body fluid associated with malabsorption of electrolytes[36]. Stool consistency evaluated in this study was used as a marker for diarrhoea. Diarrhoea with bloody stool was observed in the control group by day 3 post colitis induction unlike the *B. coriacea* fed groups which had soft but formed stool with no blood traces. Ulcerative colitis though affect the colon, may also have some extraintestinal manifestation of which anaemia is thus far the most common extraintestinal complication associated with it[37]. Treatment with *B. coriacea* was able to reverse and stabilize the levels of PCV, RBC and Hb which were decreased in the control group on induction of ulcerative colitis. Blood flow is very important in the healing process of inflammation for the supply of nutrients and growth factors[38]. The prevention of diarrhoea associated with bloody stool which could also result in anaemia as well as maintenance of the haematopoietic system further contributed to the mechanism by which *B. coriacea* enhanced the healing of experimentally induced colitis.

In conclusion, this investigation is only a preliminary study on the effect of *B. coriacea* on the healing of acetic acid induced colitis, we conclude base on the results that *B. coriacea* has a potent effect against various pathological changes caused by the administration of acetic acid. Inhibition of neutrophil infiltration as well as enhancing haematopoietic system by preventing anaemia could be likely mechanisms of action.

Conflict of interest statement

The authors of this publication declared that there is no conflict of interest.

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