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Original Research Article

Evaluation of the Effect of Cyperus Rotundus in a Murine Model of Dextran Sulphate Sodium (DSS) Induced Acute Colitis

Divakar[1], Suraj Waykole[2], Rahul Vitthal Chavan[3], Manoj Radhakrishnan[4], Sandhya Kamat[5]

[1]Assistant Professor, Department of Pharmacology, SMBT Institute of Medical sciences & research centre, Dhamangaon, Nashik, Maharashtra, India

[2]Assistant Professor, Department of Pharmacology, SMBT Institute of Medical sciences & research centre, Dhamangaon, Nashik, Maharashtra, India

[3]Associate Professor, Department of Pharmacology, SMBT Institute of Medical sciences & research centre, Dhamangaon, Nashik, Maharashtra, India

[4]Research Scientist, Multidisciplinary research unit, Seth GS Medical College & KEM Hospital, Mumbai, Maharashtra, India

[5]Professor & Head, Department of Pharmacology & therapeutics, Seth GS Medical College & KEM hospital, Mumbai, Maharashtra, India

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Corresponding author: Dr. Suraj Waykole

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Abstract

Background: Ulcerative Colitis (UC) is a chronic, debilitating condition that affects an individual throughout life and is associated with many complications. The current treatment regimen includes the use of anti-inflammatory agents such as sulfasalazine, corticosteroids and immunosuppressants like azathioprine. These drugs have limited efficacy and multiple adverse effects and hence there is a need for safer and efficacious new drugs. Cyperus rotundus (CR) is a medicinal plant used in Ayurveda for the treatment of gastrointestinal disorders. The present study examined the effect of CR in an animal model which simulates ulcerative colitis.

Objectives: To evaluate the protective effect of CR in a murine model of dextran sulfate sodium (DSS) induced acute colitis.

Methods: After IAEC approval, 48 Swiss albino mice were divided into six groups (n = 8/group) and treated as follows: Vehicle control (VC), disease control (DC), positive control (sulfasalazine - 100 mg/kg) and three test groups with CR - 200 mg/kg/day, 600 mg/kg/day and 1 g/kg/day. All 6 groups received the study drug or vehicle from day 1 to 14. The inducing agent 3% Dextran sulphate sodium in drinking water was administered from day 8 to 14 to all groups except VC. Animals were sacrificed on day 15. Colon length and colon weight-by-length ratio were assessed and analyzed using One-way Anova. Disease activity index (DAI) and colitis macroscopy were assessed and analyzed using Kruskal Wallis test. A value of $P < 0.05$ was considered to be statistically significant.

Results: CR (1 g/kg/day) significantly increased the colon length ($p<0.05$) and decreased in colon weight-by-length ratio, colitis macroscopy and DAI score ($p<0.05$) as compared to DC. Its effects were comparable to the positive control sulfasalazine.

Conclusion: Aqueous extract of rhizomes of CR exerted a protective effect in the murine model of DSS induced acute colitis.

Keywords: Cyperus rotundus, DSS, colitis.

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Introduction

Inflammatory bowel disease (IBD) is an immune mediated chronic inflammatory disease of the gastrointestinal tract, characterized by chronic relapsing inflammation affecting the individuals throughout their life [1]. It comprises Ulcerative Colitis (UC) and Crohn's Disease (CD) and results from a combination of multiple factors like environmental (smoking, diet, drugs, water pollution, geography, sleep, and stress), genetic, immune mediated (dysfunctions of innate and adaptive immune pathways) and along with gut microbiome involvement [2]. In UC, the inflammation is continuous and limited to the colon and rectum. The ulcers are superficial and involve

only the mucosal layer of the intestine. On contrast, in CD, the inflammation is discontinuous and can affect any area of the gastrointestinal tract (from the mouth to the anus). The ulcers are deep and involve all the layers of the intestinal wall. [3,4]

More than 1.4 million people have IBD in India - 2nd highest disease burden after USA. [5]

Although epidemiological data on IBD are limited in India, a population-based study conducted in Punjab, the incidence and prevalence rate were found to be 6.02 and 44.3 per 1 lakh population respectively. [6] The precise number of IBD cases among Indians is unknown, but a 2017 study estimated that more than 11 lakh people & 4 lakh people had ulcerative colitis and Crohn's disease respectively. In India UC is more common than CD. [7]

UC is a debilitating condition associated with numerous complications. It is a significant known risk factor for colon cancer development. The aim of current medical therapy is to prevent the complications of the disease itself and quickly bring about remission without the use of steroids. The treatment of UC depends upon the severity of the disease. For proctitis, topical therapy with 5-aminosalicylic acid preparation is used. Extensive colitis is treated with oral 5-aminosalicylic acid compounds and corticosteroids. If patients are not responding then immunomodulators like azathioprine and biologics like infliximab, golimumab and vedolizumab are added. These drugs are expensive and are associated with multiple adverse effects. Therefore, UC patients have reduced quality of life. [8,9] The limited safety and efficacy of the currently available treatment options warrants the search for newer agents.

Ayurveda, the Indian traditional system of medicine, has been used by numerous physicians since ancient times to treat various gastrointestinal disorders. An aqueous extract of rhizomes of Cyperus rotundus has been used in ayurveda for treatment and prevention of variety of gastrointestinal disorders including diarrhoeas of multiple etiology. It has an anti-inflammatory, anti-oxidant and anti-diarrheal properties. [10]

Acute colitis can be induced in animals by administering various chemicals like dextran sulphate sodium (DSS), 2,4,6-trinitrobenzene sulphonic acid (TNBS), acetic acid and oxazolone. Of these, DSS model is commonly used as a model to study UC due to the simplicity of its administration and ease of dosage and duration control to study varying grades of colitis. [11] The pattern of inflammation seen in this model is similar to that seen in human ulcerative colitis. Also, multiple compounds have been studied using this model and it is a relevant model to translate mouse data to human colitis. [12]

A thorough review of the literature revealed that no experimental studies have evaluated the role of Cyperus rotundus in animal models of colitis. It was therefore of interest to investigate the effect of Cyperus rotundus in a murine model of DSS induced acute colitis that simulates ulcerative colitis.

Methodology

After receiving institutional Animal Ethics Committee approval, the study was conducted according to CCSEA guidelines. The animals were housed in stainless steel grated polypropylene cages equipped with facilities for providing pelleted feed and filtered water, and husk was used for bedding. Controlled conditions were maintained with a temperature of 18°C-29°C, humidity of 30-70%, and a 12-hour light-dark cycle.

Study drug/chemicals and doses: Dextran sulphate sodium (DSS), an inducing agent, was purchased from SRL laboratories (3% in drinking water). Cyperus rotundus, aqueous extract of the rhizomes, was purchased from Shri Dhootapapeshwar Ayurvedic Research Foundation, Navi Mumbai. The extractive value was 10%. The powder was dissolved in DW to prepare a 5 mg/ml solution and administered through oral feeding tube. Sulfasalazine served as a positive control. 48 Swiss albino mice of either sex aged 6-8 weeks and weighing 18-22 g were used in this study. The animals were randomly divided into 6 groups of 8 mice in each group.

- Group 1: Normal Control (NC): 0.5 ml distilled water
- Group 2: Disease Control (DC): 3% DSS in drinking water
- Group 3: Positive Control (PC): 100 mg/kg/day
- Group 4: Cyperus rotundus low dose (CRLD): 200 mg/kg/day
- Group 5: Cyperus rotundus intermediate dose (CRID): 600 mg/kg/day
- Group 6: Cyperus rotundus high dose (CRHD): 1 g/kg/day

The doses used in the study were chosen based on the therapeutic dose of aqueous extract of Cyperus rotundus mentioned in the Ayurvedic texts. Which ranges from 1 g to 5 g per day. [13 The human dose was converted to the mouse dose using the dose conversion table based on body surface area. [14

The test drugs were administered orally to the experimental animals for the first 7 days. All groups except normal control received 3% DSS in their drinking water bottles from day 8 onwards till day 14 in addition to the orally administered test

drugs/vehicle. A digital weighing machine was used to measure the body weight of the mice at baseline (on day 8) and on days 10, 12 and 14. Similarly, stool was checked for consistency and presence of blood at baseline and on days 10,12 and 14. The disease activity index (DAI) was computed on days 10, 12 and 14 using these parameters.

On day 15, all the mice were euthanized using ketamine and restrained on the dissection board in supine position. Each mouse's ventral side was exposed, and a midline incision was made. The colon was cut at the colorectal margin and detached from the mesentery. The colo-caecal margin was then cut and the entire colon was isolated. Before sacrificing, all the animals were kept fasting for 24 hours.

Variables Assessed

Disease activity index (DAI): The DAI was calculated for each mouse on days 10, 12 and 14 of the experimental periods. The DAI was determined for each animal using this scoring system by adding the scores for weight loss, stool consistency and blood in stool on the respective measurement day as depicted in Table 1. [15]

Table 1: Disease activity index (DAI)

Score	Weight loss	Stool consistency	Blood in stool
0	None	Normal	Negative
1	1-5%	_	_
2	6-10%	Loose stool	Positive
3	11-15%	_	_
4	≥16	diarrhoea	Gross rectal bleeding

Colon length and colon weight-by-length ratio: Using a gavage needle and syringe, the isolated colon was rinsed with sterile phosphate buffer solution (PBS). Following the removal of the faeces from the colon, its length and weight were measured with a vernier calliper and a digital weighing scale, respectively. For each isolated colon, the weight-to-length ratio was computed.

Colon length and weight are important indicators of the severity of the colitis. In experimental models', acute colitis induction is associated with a reduction in the overall length of the colon. Colitis induction is also associated with oedema which results in an increase in the colon weight per centimetre of its length. [16]

Colon macroscopic grading: After the measurement of the colon weight and length, it was sliced longitudinally from distal to proximal end with the help of a scissor to expose the colitis lesions, if any. The colon was laterally opened with fine-tipped forceps, and the severity of colitis was determined macroscopically using the scoring system listed below. [17]

Macroscopic grading of colitis:

- **0 -** No ulcer and no inflammation;
- **1 -** Local hyperaemia without ulceration;
- **2 -** Ulceration without hyperaemia;
- **3 -** Ulceration and inflammation at one site only;
- **4 -** Two or more sites of ulceration and inflammation;
- **5 -** Ulceration extending more than 2 cm.

Colon histopathological examination: Each mouse's longitudinally incised colon was rolled separately using a pair of forceps. This was done by rotating the forceps and releasing them from the distal to the proximal margin. This procedure produced a specimen that resembled a "Swiss Roll," hence the name "Swiss-roll Approach" for this technique. Forceps were used to stabilise these rolled colon samples while a needle was used to transect it. These samples were then put in separate jars with 10% formalin solution and left at room temperature for 24 hours to fix the tissue. Following fixation, the colon sample was cut into sections and mounted on slides for histological analysis. The "Swiss Roll" technique helps in studying the colon in the longitudinal form, which is better than just taking transverse sections. The colon sections underwent H&E staining and were evaluated using the histological score shown in Table 2. [15]

Table 2: Histopathologic scoring system

Feature	Score	Description
Inflammation severity	0	None
	1	Mild
	2	Moderate
	3	Severe
	0	None
	1	Mucosa

Inflammation extent	2	Mucosa and submucosa
	3	Transmural
Crypt damage	0	None
	1	1/3 of crypt damaged
	2	2/3 of crypt damaged
	3	Crypts lost; surface epithelium intact
	4	Crypts lost; surface epithelium lost
Percent area of involvement	0	0%
	1	1-25%
	2	26-50%
	3	51-75%
	4	76-100%

Multiplying the total of all three histological features by the percentage area of the involvement involved yields the score. The score range is from 0 to 40.

Statistical analysis: All the results were expressed as mean ± SD. Data analysis was performed using

GraphPad InStat software (GraphPad, San Diego, CA).

Data of parametric variables (colon length and colon weight-by-length) were analysed using one-way ANOVA followed by post hoc Tukey's test.

The non-parametric variables (DAI, colitis macroscopic score and the colitis histopathology score) were analysed by Kruskal - Wallis's test followed by post-hoc Dunn test.

p value < 0.05 was considered to be statistically significant.

Results:

Disease Activity Index (DAI): The mean DAI of the disease control group on day 10, day 12 and day 14 was significantly higher ($p<0.001$) as compared to the normal control group. The mean DAI of the positive control (sulfasalazine) group was found to be significantly lower than disease control group ($p<0.001$).

There was no significant difference between the mean DAI of the low dose of Cyperus rotundus (CRLD) group and the disease control group. The mean DAI observed with the intermediate dose of Cyperus rotundus (CRID) group was significantly lower than that of the disease control group only on Day 12 ($p < 0.001$) and it was significantly higher ($p<0.05$) than the sulfasalazine group.

The high dose of Cyperus rotundus (CRHD) caused a significant decrease in the mean DAI ($p<0.001$) on day 10, day 12 and day 14. There was no significant difference between sulfasalazine group and the CRHD group. (Table 3).

Table 3: Disease activity index in various experimental groups

Group No.	Study groups(n=8/group)	Day of assessment		
		Day 10	Day 12	Day 14
1	Normal control	0	0	0
2	Disease control	4.25 ± 0.70 $	8 ± 0 $	8.85 ± 1.06 $
3	Sulfasalazine	1.62 ± 0.92 ***	3.71±0.76 ***	4.00 ± 0.82***
4	C. rotundus low dose (CRLD)	4.12 ± 0.83	7.00 ± 0.82	8.71 ± 0.76
5	C. rotundus intermediate dose (CRID)	3.62 ± 0.92	6.12±0.83*** #	8.16 ± 0.75
6	C. rotundus high dose (CRHD)	2.00 ± 0.76***	4.12 ± 0.83 ***	5.00 ± 0.76 ***

All values are expressed as mean ± SD. $ p < 0.05 vs Normal control group, ***p < 0.001 vs Disease control group, # p < 0.05 vs Sulfasalazine group, using Kruskal Wallis test followed by post-hoc Dunn's test.

Colon length: The mean colon length was significantly lower ($p<0.001$) in the disease control group as compared to the normal control group. The mean colon length was significantly higher in the sulfasalazine group ($p<0.001$) as compared to the disease control group. The mean colon length in the group that received CRLD was not significantly different than that of the disease control group. However, there was a significant difference in the mean colon length of CRHD ($p<0.001$) and CRID groups ($p<0.05$) as compared to the disease control group.

The mean colon length of the CRID group was significantly lower ($p<0.05$) than that of the sulfasalazine group. There was no significant difference between CRHD group and sulfasalazine group. (Table 4).

Colon weight/length ratio: The mean colon weight/length ratio was significantly higher in the disease control group as compared to the normal control group ($p<0.001$). The sulfasalazine group showed a significantly lower mean colon weight/length ratio ($p<0.001$) as compared to the disease control group. The CRLD group was not significantly different than the disease control group. On the other hand, the mean colonic weight/length ratio in both CRHD ($p<0.001$) and CRID ($p<0.05$) groups were significantly lower as compared to the disease control group. The mean colonic weight/length ratio of CRID group was significantly higher ($p<0.001$) than that of the sulfasalazine group. There was no significant difference between CRHD group and sulfasalazine group. (Table 4).

Colon macroscopic grading of colitis: The mean colon macroscopic grading score was significantly higher in the disease control group as compared to the normal control group ($p<0.001$). The sulfasalazine group showed a significantly lower mean colon macroscopic grading score ($p<0.05$) as compared to the disease control group. Both CRID and CRLD groups were not significantly different than the disease control group. On the other hand, the mean colon macroscopic grading score in CRHD ($p<0.05$) group was significantly lower as compared to the disease control group. There was no significant difference between CRHD group and sulfasalazine group. (Table 4).

Colon histopathology score: The mean colon histopathology score was significantly higher in the disease control group as compared to the normal control group ($p<0.001$). The sulfasalazine group showed a significantly lower mean colon histopathology score ($p<0.001$) as compared to the disease control group. The CRLD group was not significantly different than the disease control group. The mean colon histopathology scores in the CRID ($p<0.01$) group were significantly lower as compared to the disease control group but was significantly higher ($p<0.001$) than that of the sulfasalazine group. On the other hand, the mean colon histopathology score in the CRHD group was significantly lower ($p<0.001$) than the disease control group, in addition there was no significant difference between CRHD group and sulfasalazine group. (Table 4).

Table 4: Effect of the test drugs on the colon length, colon weight/length, macroscopic grading of colitis, and histopathology score.

Group no.	Test group	Colon length (cm).	Colon weight/length (mg/cm)	Macroscopic grading of colitis	Histopathology score
1.	NC	8.46 ± 0.18	18.69 ± 1.41	0	0
2.	DC	6.01 ± 0.19 $	31.92 ± 0.51 $	3.57 ± 0.53 $	17.14 ± 1.34 $
3.	PC	7.48 ± 0.13 ***	21.87 ± 0.24 ***	1.57 ± 0.53 *	7.71 ± 1.11 ***
4.	CRLD	6.11 ± 0.13	31.46 ± 0.63	3.43 ± 0.53	16.14 ± 1.34
5.	CRID	6.31 ± 0.14 * #	30.47 ± 0.25 * #	3.00 ± 0.63	15.00 ± 0.89 ** #
6.	CRHD	7.30 ± 0.13 ***	22.43 ± 0.37 ***	1.62 ± 0.52 *	8.00 ± 0.92 ***

NC- Normal Control, DC- Disease Control, SLZ- Sulfasalazine, CRLD- C. rotundus low dose, CRID- C. rotundus intermediate dose, CRHD- C. rotundus high dose, All results expressed in mean ± SD, $ $p < 0.05$ vs Normal control group, *** $p < 0.001$ vs Disease control group , # $p < 0.05$ vs Sulfasalazine group.

Colon length and colon weight/length were analyzed using one-way ANOVA followed by post hoc Tukey's test. Macroscopic grading score and histopathology score were analyzed using Kruskal Wallis test followed by post-hoc Dunn's test. Histopathological effects of Cyperus rotundus on the dextran sulphate sodium (DSS – 36000 to 50000 MW) induced acute colitis (40x), Figure 1.

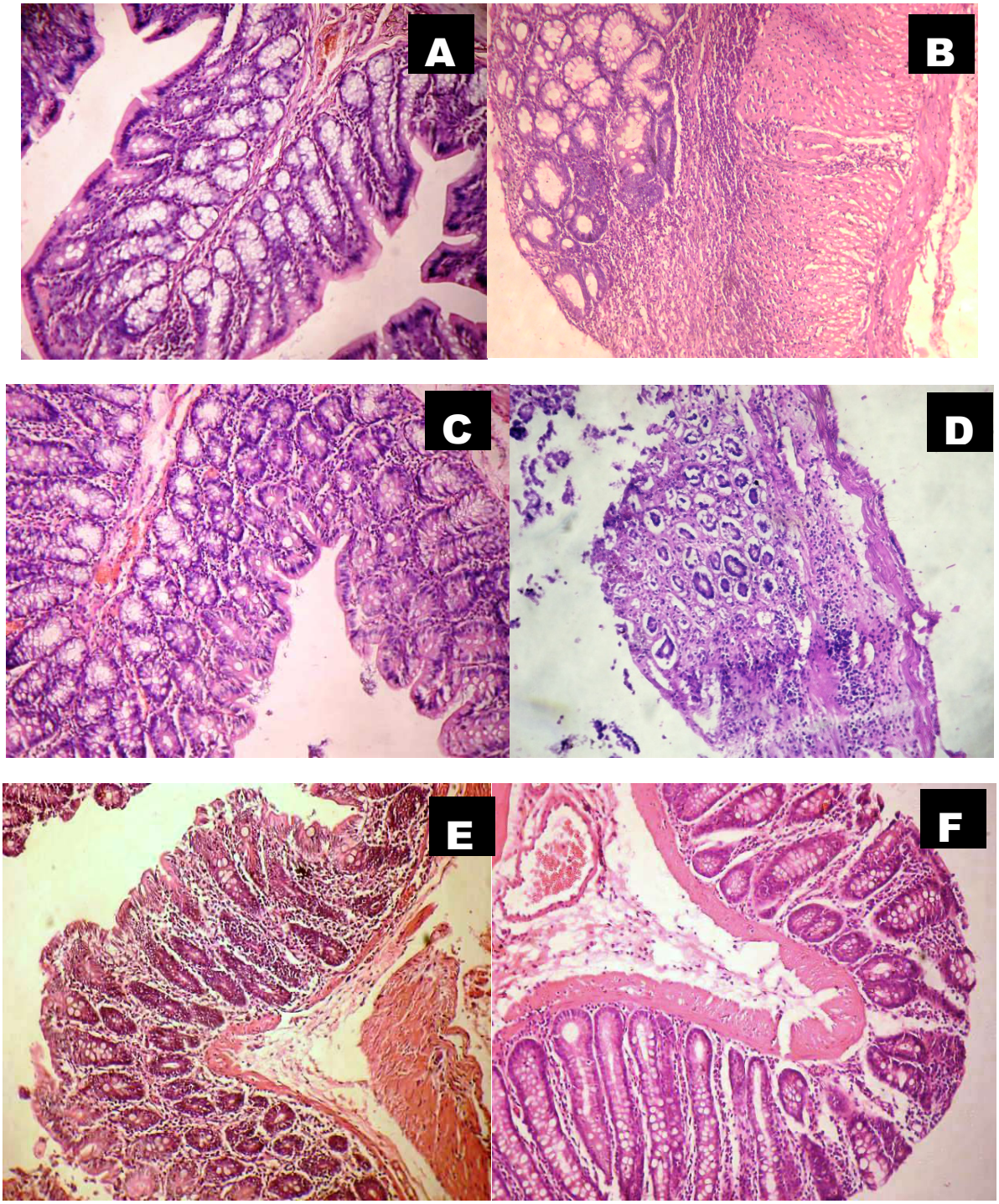

Figure 1: Colon histopathologic examination:

A. Normal control showing colon depicting normal crypt architecture with epithelial lining.
B. Disease control treated with DSS showing crypts completely damaged along with epithelial erosion and dense lymphocytic infiltration.
C. Intermediate dose of Cyperus rotundus with DSS showing Crypt distortion and lymphocytic infiltration.
D. High dose of Cyperus rotundus with DSS showing near-normal crypt structure and minimal mucosal lymphocyte infiltration.
E. Positive control sulfasalazine with DSS showing near-normal crypt structure and minimal mucosal lymphocyte infiltration.
F. Low dose of Cyperus rotundus with DSS showing almost completely damaged crypts and dense lymphocytic infiltration.

Discussion

Present study evaluated the effect of the aqueous extract of rhizomes of Cyperus rotundus in a murine model of dextran sulphate sodium (DSS) induced acute colitis. This study was conducted in

Swiss albino mice as compared to other animal models; mice have many advantages. The mouse and human colon are quite similar in physiology and anatomical structures. [18] The human gut microbiome is functionally similar to its mouse counterpart. [19,20]

Intestinal inflammation can be induced in various ways, of the, the DSS induced colitis model has many advantages over other animal models. Firstly, the concentration of the inducing agent can be easily changed in this model to produce varying grades of colitis. The clinical features seen in the acute phase of DSS induced colitis include loss of weight, diarrhea, occult blood in stools and frank bleeding per-rectum. Histological features seen in DSS induced colitis in mice include degeneration of epithelium, infiltration of inflammatory cells in the mucosa and sub-mucosa, inflammation of the crypts and necrotic changes. Both the clinical and histological features are similar to that observed in human ulcerative colitis. Thus, it is a relevant model to translate mice colitis data to human ulcerative colitis.[21]

Once the model was confirmed, the vehicle and study drugs were administered and the effects were assessed. It was found that mice in the disease control group showed significantly higher disease activity index (DAI) on days 10,12 and 14. Similarly the disease control group also showed a significantly higher colon weight by length ratio, colon macroscopy grading score & colon histopathology score. These findings indicated that DSS had induced acute colitis and were similar to other studies done by Axelsson et al. [22] and Clapper et al. [23] have used DSS models.

Only the high dose and the intermediate dose of Cyperus rotundus caused significant alleviation of DSS-induced colitis and of these only the high dose was comparable to sulfasalazine.

Only one study conducted by Johari et al. has examined the clinical effects of Cyperus rotundus earlier. However, they studied the chloroform extract of tubers of Cyperus rotundus in the di nitro benzene sulphate model of acute colitis using Sprague Dawley rats.

The researchers observed that pretreatment with the chloroform extracts of tubers of Cyperus rotundus significantly prevented the weight loss of the animal, shortening of colon and reduced the colon weight, as was observed in our study. However, they did not study the disease activity index and histopathological effects of the extract of Cyperus rotundus. [24]

The present study is the first study to examine the effect of the aqueous extract of Cyperus rotundus in an animal model of acute colitis. One of the strengths of this study was that not only were the colon-based variables like colon length, weight by length ratio, macroscopic grading assessed but in addition the disease activity index and histopathology was also studied.

It is believed that ulcerative colitis is caused due to an imbalance between the intestinal microbiota and mucosal immunity which results in excessive intestinal inflammation. [25] The rhizomes & tubers of Cyperus rotundus have multiple bio-active compounds like alkaloids, flavonoids, tannins, glycosides and sesquiterpenoids which have been demonstrated to have anti-inflammatory, anti-diarrheal and anti-oxidant properties. [26,27] These bioactive compounds might be responsible for the plant's protective effects against colitis. In another study by Johari et al. demonstrated that the chloroform extract of Cyperus rotundus decreased the expression of the colonic cytokines (IL-4, IL-6, IL-12 and IFN-gamma), myeloperoxidase (MPO) and superoxide dismutase (SOD). [28] Sharma et al. has reported the antimicrobial properties of ethanolic extract of rhizomes of Cyperus rotundus. [29] In the present study the effects of the aqueous extract on anti-inflammatory, and anti-oxidant biomarkers were not studied.

This study has laid a foundation for further research wherein the effect of the aqueous extract of Cyperus rotundus can be studied on various inflammatory and antioxidant biomarkers and on the gut microbiome. It would also be worthwhile to study the effects of the aqueous extract in other animal models of acute as well as chronic colitis.

Moreover, as the aqueous extract of Cyperus rotundus is already being prescribed to patients by Ayurvedic physicians, clinical trials and animal research can be carried out concurrently to validate our findings in patients of ulcerative colitis.

The data generated through such animal and clinical studies will lead to the development of such safe and affordable formulations from our traditional system of Indian medicine for the treatment of ulcerative colitis.

Conclusion

As compared to the disease control group, the high dose Cyperus rotundus group had significantly better effects on all the variables ($p<0.05$). Its effects on all variables were comparable to the positive control sulfasalazine group. In comparison to the disease control the intermediate dose of Cyperus rotundus reduced the DAI only on day 12 but significantly prevented the shortening of colon, decreased colon weight-by-length ratio, and colon histopathology score. However, the effects of intermediate dose of Cyperus rotundus were not comparable to the sulfasalazine group. The low dose Cyperus rotundus could not significantly alleviate the colitis.

To conclude, the high dose (1g/kg/day) of aqueous extract of rhizomes of Cyperus rotundus showed protective effect and was comparable to the standard dose of sulfasalazine in DSS induced acute colitis. Further studies need to be conducted not only to investigate the mechanism of action of Cyperus rotundus in colitis but also study its effect in chronic colitis.

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