Journal of Medicinal and Chemical Sciences 6 (2023) 1915-1924

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Anti-Inflammatory Effect of Curcuma Longa on Ulcerative Colitis Caused via AcOH in Rats

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ARTICLE INFO

Article history

Receive: 2022-12-15
Received in revised: 2023-02-17
Accepted: 2023-02-20
Manuscript ID: JMCS-2301-1932
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Nenad Ignjatovic

DOI:10.26655/JMCHEMSCI.2023.8.20

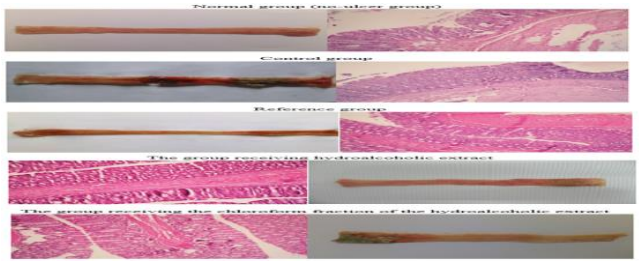
KEYWORDS

Anti-inflammatory
Curcuma longa
Ulcerative colitis
AcOH
Rat

ABSTRACT

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting inflammatory disorder of the small intestine and colon. The purpose of this research was to investigate the anti-inflammatory efficacy of turmeric plant on ulcerative colitis caused by AcOH in rats. This research is a single-blind controlled trial for outcome assessor conducted on 70 male Wistar rats since the beginning of 2022 in the laboratory of the Faculty of Medicine. A total of 72 male Wistar rats with a weight range of 180-220 were included in the study. The selected mice were bred in the animal cage of the college and were reared under similar lighting conditions, humidity, and nutrition. Then, the samples were randomly placed in 9 groups (8 samples in each group) by Excel software. Three doses (50, 100, and 200 mg/kg) of the extracts were effective in reducing the weight of the distal colon (8 cm) as a marker of tissue inflammation and edema. Three doses (50, 100, and 200 mg/kg) of hydroalcoholic extract and two more doses of chloroform fraction (100 and 200 mg/kg) were effective in reducing ulcer severity and area, and in reducing the severity and extent of mucosal inflammation, crypt damage, invasive involvement, and total colitis index. The chloroform fraction (50 mg/kg) was ineffective in reducing the evaluated colitis component compared to the control group. This shows that hydroalcoholic extract and chloroform fraction are effective in the treatment of experimental colitis. It can be attributed to the same main compounds, flavonoids, and biophenols. Efficacy was already detectable at low doses of the chloroform fraction. Therefore, the presence of a very potent active ingredient in the rhizome is compelling.

GRAPHICAL ABSTRACT



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Introduction

Ulcerative colitis and Crohn's disease are among the most important inflammatory bowel diseases. The underlying causes of these diseases are unclear, but the active immune system in the intestines in the face of intestinal flora can be the possible cause of inflammation in this disease. The prevalence of ulcerative colitis is higher than Crohn's disease. The highest prevalence of this disease has been observed in North America and Europe. The onset of ulcerative colitis is associated with inflammation limited to the mucosa, which usually starts from the rectum, and then affects the entire colon [1]. In healthy people, the epithelial surface in the intestine is covered by a layer of mucin, which is the first line of defense because it creates a barrier against the epithelial membrane and microbes. In ulcerative colitis patients, the synthesis and sulfation of a subtype of mucin called mucin-2 (MUC-2) is reduced, which causes defects in the immune system, and thus tight junctions in the gut. In addition, epithelial cells secrete antimicrobial peptides called defensins in all people, which prevents bacteria from invading the epithelium. In ulcerative colitis patients, we have excessive beta-defensin production [2]. The peak age for onset of this disease is between 30-40 years and the highest incidence rate is seen in Northern Europe with a rate of 24.3 per 100000, Canada with a rate of 19.2 per 100000, and Australia with a rate of 17.4 per 100000 [3].

Approximately 8-14% of patients have a family history of inflammatory bowel disease, and their first-degree relatives are 4 times more at risk than others [3]. The drug of choice in these patients is determined based on the severity of the disease and its symptoms, so that in mild to moderate patients, Mesalamine, or 5-ASA is an anti-inflammatory drug that controls the synthesis of prostaglandins and leukotrienes. It can be administrated and used orally or rectally. In these patients, corticosteroids are used to improve the active phase of the disease [3]. In severe to the advanced cases, the family of thiopurines, which include Azathioprine or 6-Mercaptopurine, and methotrexate, which are effective in inhibiting mitosis, and in severe and acute cases, anti-TNF drugs, including Infliximab that are effective in inhibiting inflammation, are used [3]. These drug categories and the mechanism known so far in this disease suggest that inflammatory conditions are involved in the pathophysiology of this disease.

Although people use different herbal medicines daily for their diseases, the effectiveness of a limited number of these medicines has been confirmed in modern medical science. One of these medicines is Curcuma Longa. This perennial plant grows abundantly in the tropical area of Asia and is widely used as a powder to color and flavor food. Furthermore, this plant is used for medical purposes, especially in India. For example, its powder is used in combination with slaked lime in the home treatment of ankle sprains and the resulting swelling. Pharmacodynamic studies by Indian researchers have investigated the anti-inflammatory effects of this plant [4]. The study conducted by Stephanie Maxine Ross showed the effect of this plant with ibuprofen in reducing pain and increasing the ability of patients with arthritis, and the pain was significantly reduced in both groups. Likewise, patients using ibuprofen had high gastrointestinal side effects [5]. In another clinical trial conducted by Henrotin *et al.*, the effect of this plant extract on reducing the pain of osteoarthritis patients was investigated. It was reported that in addition to have no severe side effects, this drug is effective in the disease activity index and it is associated with the reduction in patients' pain [5].

Julie S. Jurenka reviewed the anti-inflammatory properties of Curcuma Longa [6, 7]. Moreover, in another article by Bharat B Aggarwal *et al.*, the results showed that since many chronic diseases have inflammation and the long-term use of anti-inflammatory drugs has many side effects, and this plant has several inflammatory pathways. Therefore, more studies are needed to investigate the long-term effects of this drug [8]. Another review study conducted by Moshe Schaffer *et al.*, reported that strong evidence has been found in chemical and animal studies that this plant has beneficial and anti-inflammatory properties. Also, it referred to the known ROS and NF-κB

pathways that Curcuma Longa plant affects them and through which suppresses the pro-inflammatory state in the body [9]. In another review study by Fernando Cunha Neto, it was stated that this drug can be used in the treatment used as an adjuvant for these diseases owing to the expensive cost for treatment of ulcerative colitis and Crohn's disease as well as the effectiveness of this plant in inflammatory conditions and its antioxidant properties [10].

Given the mentioned pharmacological effects of this plant and the high incidence of ulcerative colitis disease and the importance of treatment and helping to improve the life quality of these patients, this study aims to investigate this plant by inducing this disease in a laboratory. If this study yields positive results for this plant and complementary studies confirm them, it can be introduced for making suitable pharmaceutical formulations for this group of patients. Since turmeric is widely used as a flavoring agent in food and because of its medicinal properties, it was thought worthwhile to investigate the protective effects of turmeric (Curcuma longa, CL) on acetic acid-induced colitis in a rat model of IBD with special emphasis on colon ulcers.

Martials and Methods

Pharmacognosy

1. Preparation of plant rhizome (Rhizomes develop from axillary buds and grow horizontally).
2. Identification of the plant's rhizome by the pharmacognostic specialist of the project.
3. Preparation of rhizome hydroalcoholic extract by percolation method and its chloroform fraction.
4. Determining the dry matter concentration of the extract or fraction, preliminary phytochemical investigation, and quality controls of the extract.

To prepare the hydroalcoholic extract, the desired powder was soaked in EtOH-H_2O at a ratio of 3 to 7 for 24 hours, and for the pure extract, infiltration was done with water ethanol (for 48 hours). The extract was then filtered and cut into two halves. The first part was evaporated under reduced pressure to produce a semi-solid product of 7.71%, which is basically the hydroalcoholic extract. The second part of the extract was poured into a triplet containing 100 ml and the amount of each fraction was collected and evaporated until a semi-solid product of 67.96% was obtained, which is the chloroform fraction of the hydroalcoholic extract [11]. The rats were kept in the laboratory for 24 hours, and then they underwent a light anesthesia with ether and 2 cc of 3% AcOH was entered into the colon as an enema with a plastic tube 8 cm long and 2 mm in diameter [12].

Intervention

1- In Group 1 (normal): 1 mg/kg of normal saline was given orally and colitis was not induced in this group.
2- In Group 2 (negative control group): 1 mg/kg of normal saline was given orally and colitis was induced in this group.
3- In Group 3 (positive control group): Prednisolone 4 mg per kg was given orally for 5 days, the first dose of which was 2 hours before the onset of colitis.
4- Groups 4, 5, and 6: Three doses of hydroalcoholic extract of rhizomes of 50, 100, and 200 mg/kg were orally administered to rats 2 h before colitis onset and continued for 5 days.
5- In the Groups 7, 8, and 9: Similar to the previous group, the chloroform fraction obtained from the hydroalcoholic extract with three doses of 50, 100, and 200 mg per kg was given orally to the rats 2 hours before the colitis development and continued for 5 days.

These groups were removed 24 hours after taking the last dose of the victim's medicine and the abdomen was perforated and the large intestine was exposed. An 8 cm long, 2 cm proximal to the anus distal colon was resected and washed with normal saline. After weighing with a laboratory digital scale based on mg, they are used for macroscopic studies in this way:

The ulcer severity was evaluated using the Morris criterion [13], as explained in the following:

0: No transformation.
1: Mucosal edema only.

2: Mild swelling of mucous membranes, mild bleeding, or mild atrophy.
3: Moderate swelling, bleeding ulcer, or atrophy.
4: Sever ulceration, atrophy, swelling, and tissue necrosis.
Mean surface area of ulcers in cm^2.= U_A
Mean severity of ulcers. = U_S

The ulcer area is evaluated by Fiji-win 32 software. For the accurate comparison of the effect of the used drugs, the Ulcer Index is obtained from the calculation of the sum of UA+US. Likewise, total colitis index is obtained by calculating the sum of inflammation intensity, inflammation volume, and crypt damage. After macroscopic studies, the target tissues were cut into two uniform parts and one part was kept in 10% formalin for one hour and at least one tissue sample was prepared from each animal and microscopic sections were taken from them for the next steps and in a standard way and the pathology was prepared by the pathologist. The tissues were examined in terms of the level of leukocyte infiltration, the intensity, and level of mucosal inflammation, as well as the extent of cryptic damage of the mucosal tissue [12]. Cooper *et al.* and Dieleman *et al.* reported inflammation and crypt damage were assessed by H&E staining was evaluated using the defined rating system is calculated.

Ulcer level evaluation method

After removing the distal colon (at a distance of 2 cm from the proximal anus with a length of 8 cm) [11], the tissue was cut in the middle with scissors in the longitudinal direction of the tissue, washed with normal saline, and weighed in the wet state using a scale. It was measured digitally in a laboratory that has a very high accuracy. The colon weight is a variable affected by inflammation and edema, and if it is weighed according to the specified length (8 cm) and in a wet state, it can be a useful index to examine the colitis severity. Then, the tissue was spread on the work table. A color and digital photo was taken of the colon tissue, and then ulcer surface was calculated by Fiji-win -32 software (NIH Image for the Macintosh, 2004) [12-16].

Evaluating the myeloperoxidase activity in colon tissue

Another part of the colon tissue was placed in Falcon tubes numbered in advance and prepared for this purpose and immediately placed in a nitrogen bath to freeze quickly and all samples were stored in frozen conditions at -70 °C until their collection. On the day of the experiment, the solutions and reagents to be tested were initially prepared and the MPO activity was calculated in terms of units per gram of tissue and determined by the following method. First, the studied tissue sample was homogenized in 10 mM potassium phosphate buffer solution with pH=7 containing 0.5% hexadecyltrimethylammonium bromide (with the help of a homogenizer). Then the sample was centrifuged at a speed of 20,000 g for 30 minutes at 4 °C, and H_2O_2 (0.1 mM) and O-dianisidine Hcl (1.6 mM) were added to the supernatant solution of the centrifuged tubes. Finally, absorbance of the sample in wavelength of 450 nm was checked. Then, the level of MPO activity was evaluated and reported as U/100 mg of wet colon tissue.

Results and Discussion

Clinical results

Table 1 lists the clinical results of colitis induction. Colonic infusion of AcOH leads to diarrhea and weight loss in mice. Finally, intracolonic administration of AcOH resulted in significant weight loss ($P < 0.01$) in all groups. There was the greatest weight loss in the AcOH group. However, animals treated with curcuma longa lost less weight ($P<0.05$).

Macroscopic evaluation

By injecting 4% AcOH into the large intestine, macroscopic damage was find out in the colon of mice compared with the normal group. Results showed that no alterations were observed in the normal group, suggesting that the surgery and repositioning had no effect on the experiential results. Treatment with prednisolone as a corticosteroid reference drug reduced wound score, wound area (cm^2), wound index, and colon wet weight from 8 cm ($p<0.001$), as presented in

Table 1. All normal doses and oral treatment with chloroform reduced colon weight by 8 cm (mg) compared with controls (p<0.001). Lesion severity, wound area, hemorrhage, and wound index were significantly reduced by moderate and high doses (100 and 200 mg/kg) of both tested extracts, whereas low doses of chloroform (50 mg/kg) kg) showed a significant difference in the evaluation results. Parameters are provided in Table 1.

Table 1. Effect of hydroalcoholic drugs (50, 100, and 200 mg/kg) and their chloroform ratios (50, 100, and 200 mg/kg) of Corcoma lunga rhizome on the macroscopic component of AcOH-induced colitis in rats

Entry	Groups	Ulcer index	Ulcer area	Ulcer severity	Weight of Distal Colon (mg)
1	Normal	0.0±0.0	0.0±0.0	0.0±0.0	723.7±29.8
2	Negative group	8.8±0.7	5.4±0.7	4.0±0.0	1901.1±28.1
3	Positive group	2.3±0.1**	1.4±0.2***	1.0±0.2***	821.7±17.9***
4	Hydroalcoholic 50	2.9±0.5**	2.3±0.4	2.1±0.2***	961.1±70.1***
5	Hydroalcoholic 100	4.1±0.8**	2.1±0.3***	2.0±0.4***	911.7±42.9***
6	Hydroalcoholic 200	3.3±0.5**	1.5±0.2***	1.7±0.3***	831.2±5.8***
7	Chloroform 50	6.8±0.4**	4.3±1.0	2.5±0.4	1269.1±100.2
8	Chloroform 100	4.7±0.7**	2.5±0.3***	1.9±0.3***	943.4±48.5***
9	Chloroform 200	3.2±1.3**	1.6±0.1***	1.3±0.2	852±37.2***

Data are expressed as mean±SEM.

***p<0.01 and *** p < 0.001 indicate significant difference vs. control.*

Pathological examination

In the normal group, no pathological and histological lesions were observed, but mice with colitis caused by exposure to AcOH and normal saline treatment (control) showed destruction, edema, necrosis, hemorrhage of the epithelium, inflammatory cell infiltration, crypt damage, and wound in the layer reported the submucosal in the mucosa according to Table 2. Treatment with prednisolone displays a considerable reduction in inflammation extent (p<0.01) and inflammation severity (p<0.01). The reference drug was further effective in reducing crypt damage (p<0.001) and total colitis index (p<0.01) after oral administration. Administration of hydroalcoholic extract was consistently impressive in reducing crypt damage, inflammation extent, histopathology scores, including inflammation severity, and total colitis index (P<0.01) (Table 2 and Figure 2).

Measurement of MPO activity

MPO activity was controlled in groups receiving hydroalcoholic extracts (100 and 200 mg/kg), prednisolone (4 mg/kg) (p<0.001), and chloroform fraction (200 mg/kg) (Table 3). MPO activity was also associated with a decrease (at least p<0.05) in the groups given the hydroalcoholic extract (50 mg/kg) and the chloroform portion (100 mg/kg), whereas 50 mg/kg A significant reduction was seen in rats treated with differences were found (Table 3 and Figure 1).

Curcuma longa has been drawing in consideration as a low-cost natural product. Numerous reports have emerged that this product has multiple biological activities. The purpose of this research was investigating the anti-inflammatory efficacy of turmeric plant on ulcerative colitis caused by AcOH in rats, though a few scholars are skeptical approximately its effectiveness [17]. Under pathophysiological conditions, the balance between cell proliferation and cell death is frequently improved, conclusively leading to loss of tissue homeostasis. Inadequate apoptosis development may contribute to the development of various colonic diseases such as ulcerative colitis, Crohn's disease, and cancer [18]. The acute ulcerative colitis (UC) model achieved from colonic infusion with AcOH is a repeatable and simple model that has many resemblances with human colitis. We illustrated that *Curcuma longa* can counteract AcOH-induced UC *via* reducing inflammatory responses and oxidative stress levels and by usage other feasible mechanisms such as stabilization of epithelial cell apoptosis conditions, up-regulation, and MAPK p38 down-regulation.

Table 2: Effect of hydroalcoholic extract of Corcoma lunga rhizome and its chloroform portion on pathological parameters of AcOH-induced colitis in rats

Groups	Inflammation severity (0-3)	Crypto damage (0-4)	Inflammation Extent (0-3)	Total colitis index (0-10)
Normal	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Negative group	3 (3)	4 (4)	3 (3)	9 (9)
Positive group	1 (0-1)**	2 (0-2)***	2 (0-2)**	3 (1-5)**
Hydroalcoholic 50	2 (0-3)	2 (1-4)	2 (0-3) *	7 (4-9) *
Hydroalcoholic 100	1 (0-3) **	3 (0-4)	2 (0-2)**	6 (1-7) *
Hydroalcoholic 200	2 (0-3) **	2 (0-4) ***	1(0-2)	5 (1-8) **
Chloroform 50	3 (2-3)	3 (1-4)	2 (2-3)	9 (5-10)
Chloroform 100	3 (2-3)	2(0-4) *	2 (0-3) *	8 (2-9) **
Chloroform 200	1 (0-2) **	3 (0-4) *	2 (0-3)**	4 (1-7) **

Data are expressed as medians (ranges).

**p<0.05, ** p<0.01, and *** p<0.001 significant differences compared with controls are indicated (Mann-Whitney U test).*

Table 3: Effect of hydroalcoholic extract of Corcoma lunga rhizome and its chloroform portion on MPO activity in AcOH-induced colitis in rats

Groups	Normal	Prednisolone4	Hydroalcoholic 50	Hydroalcoholic 100	Hydroalcoholic 200	chloroform 50	chloroform 100	chloroform 200
MPO activity	4.2±0.1	1.2±0.1***	3.5±0.3**	3.2±0.2**	1.8±0.1***	4.9±0.3	3.9±0.3*	2.7±0.1***

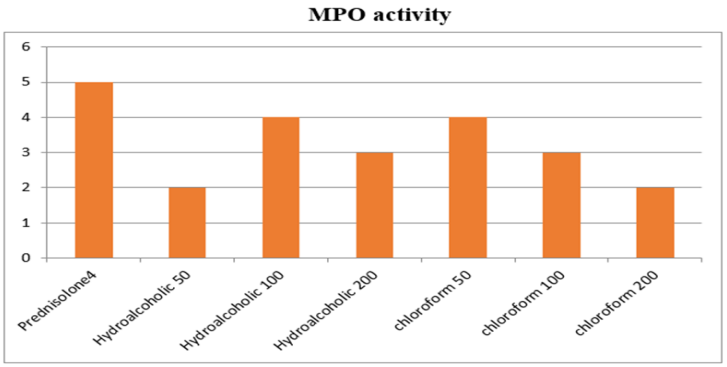

Figure 1: Myeloperoxidase (MPO) activity (E/g) in colon tissue of treated rats under different exposure conditions to different amounts of prednisolone, hydroalcoholic extract, and chloroform fractionation

Recent studies have shown that the AcOH-induced colitis model for screening drugs with anti-colitis activity is both rapid and reproducible, and resembles the pathological and clinical features of human ulcerative colitis [19, 20]. Briefly speaking, the outcomes ascertain the performance of this procedure since acute and irreversible colitis was established in laboratory rats. Prednisolone was utilized as a reference drug to define the efficacy of Curcuma longa and the results showed protection considering macroscopic and microscopic factors for the used drugs. The similar results were acquired by hydroalcoholic extract (50, 100, and 200 mg/kg) and chloroform (100 and 200 mg/kg) compared with control group. Assessment of morphological damage and tissue changes are usually used to estimate the severity of inflammation. A good

predictor of acute inflammatory response, MPO reflects neutrophil activity. In our research, MPO activity was increased in AcOH-treated mice, confirming the inflammation development.

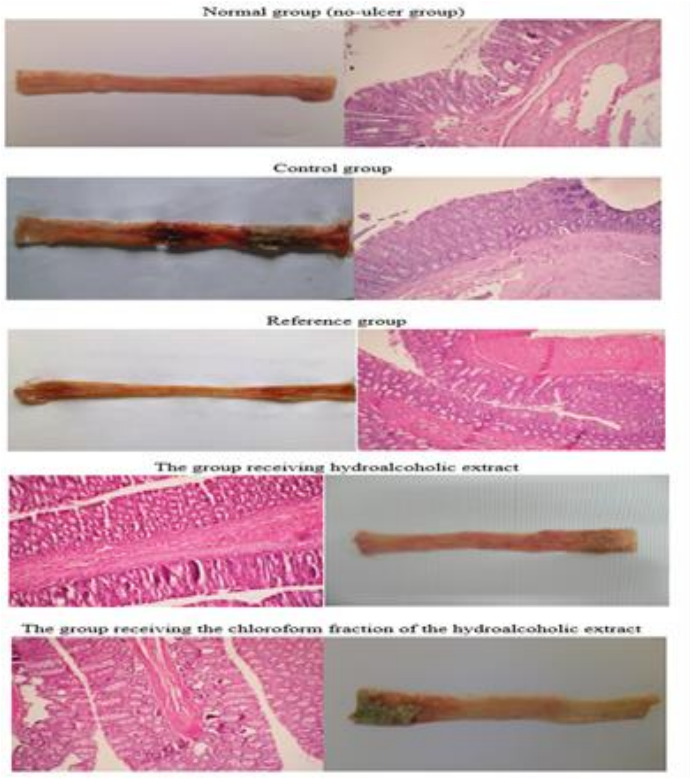

Figure 2: Microscopic and macroscopic images of different groups

This increased MPO activity was protection by histological discovery showing hemorrhagic necrosis, goblet cell depletion, mucosal ulceration, and inflammatory cell infiltration in the colon of colitis mice.

The same to the recent research results, we showed that Curcuma longa treatment was significantly associated with a drop in histological scores and MPO activity, confirming the anti-inflammatory effect of curcuma longa [21]. Our results are conforming to prior reports from other experimental models of ulcerative colitis [22, 23]. Curcuma longa has a wide range of biological activities such as anti-inflammatory, anti-tumor, and antioxidant activities. It Daro as an anti-inflammatory and anti-cancer drug is under clinical evaluation. Furthermore, Curcuma longa has recently been shown to act as an important anti-apoptotic mediator in several cellular events [24]. By injecting AcOH into the large intestine, a macroscopic lesion was observed in the mouse colon compared to the (normal) group. The results did not show any change in the normal group, and this indicates that the surgery and displacement did not interfere with the experimental results.

Researchers theorize that inflammation is resolved by regulating the accumulation of macrophages at sites of inflammation in the colon. Zhang *et al*. reported that Curcuma longa controlled 2,4,6-trinitrobenzenesulfonic acid - induced colitis via activating PPAR-γ and caused long-term survival and reduced the macroscopic level of colitis in mice with IBD. They showed that curcuma longa together with dexamethasone can rectify the expression of PPAR-γ and inhibit the PGJ2 and COX-2 expression [25].

The IBD treatment makes a speciality of lowering infection and in the end relieving symptoms. Currently, the clinical efficacy of immunosuppressive and anti-inflammatory drugs is not good. Curcuma longa is notice an effective treatment for IBD owing to its considerable immunogenic and anti-inflammatory effect. Curcuma longa may mediate anti-inflammatory effects through the following targeted molecular

pathways [26]. The results of this study showed that the size of the lesion, wound location, bleeding, and wound indices were significantly reduced with medium and high doses (100 and 200 mg/kg), while the low dose of chloroform (50 mg) decreased had shown significant Curcuma longa reduces inflammation by reducing genes related to oxidative stress and fibrogenesis pathways. PI3K activity and AKT phosphorylation lead to reduced cell death. In addition, curcuma longa upregulated neutrophils and decreased PI3K and AKT phosphorylation levels [27]. In the present study, we showed that MPO activity in the group receiving hydroalcoholic extract (100 and 200 mg/kg) and chloroform fraction (200 mg/kg) and prednisolone (4 mg/kg) was associated with a decrease. The activity of myeloperoxidase (MPO) in mice with colitis was associated with a decrease after the administration of curcuma longa with a significant difference. Therefore, oxidative stress can significantly reduce the cytokine cascade and colitis response [28].

According to reports of Shukla *et al.*, after consuming curcuma longa, the level of superoxide dismutase (SOD) in the serum of mice increases, which shows that curcuma longa has excellent anti-inflammatory and antioxidant efficacy. Curcuma longa can scavenge intracellular oxygen free radicals, regulate lipid peroxidation in tissues, and protect SOD activity in tissues. Therefore, it has a good anti-inflammatory effect in treating ulcerative colitis. Curcuma longa plays a beneficial protective role in ulcerative colitis by balancing oxidant/antioxidant level. However, large-scale multicenter clinical trials are requirement to confirm its safety and efficacy. We hope that subsequent reports on Curcuma longa will prepare new drug investigation outlook for the IBD treatment and betterment.

Conclusion

Nowadays, curcuma longa is broadly utilized in the paint, cosmetics, food industry, etc. Current studies show that curcuma longa has high pharmaceutical advantage containing anti-fibrosis, anti-apoptotic, anti-tumor, antioxidant, anti-inflammatory, and immune system regulation. System and other impacts can be utilizing to remedy various kinds of sicknesses from spectrum such as ulcerative colitis (UC), a nonspecific inflammatory bowel disease including Crohn's disease (CD), and inflammatory bowel disease (IBD). Drug treatments are often of limited efficacy and are associated with side effects. Various basic and clinical studies have shown that Curcuma longa can be effective in treating and improving IBD patients.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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HOW TO CITE THIS ARTICLE
Wiwik Herawati Waluyo, Ratri Maya Sitalaksmi. Anti-Inflammatory Effect of Curcuma Longa on Ulcerative Colitis Caused via AcOH in Rats. *J. Med. Chem. Sci*., 2023, 6(8) 1915-1924
DOI: https://doi.org/10.26655/JMCHEMSCI.2023.8.20
URL: http://www.jmchemsci.com/article_167548.html