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Original Article

Histological Comparison of Effectiveness of Short Term and Long Term Consumption of Crocus Sativus L. (Saffron) Stigma Total Extract on Total Colitis Index in Experimental Model of Ulcerative Colitis in Male Rats

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Abstract

Background: Saffron and its active components carotenoids display antioxidant, anti-inflammatory and anticarcinogenic activities. The purpose of this study was to evaluate histological effectiveness of short- and long- term consumption of *Crocus sativus* L. (Saffron) stigma total extract on colitis index in experimental model of Ulcerative Colitis(UC) in male Sprague-Dawley rats. **Methods and Materils:** Thirty-two male rats were divided into four groups as saffron, colitis, short term treatment (after acetic acid induced-colitis rats treated with 150 ppm for 6 days); long term treatment (saffron were gavaged 21 days before colitis induction and continued for 6 days after acetic acid induced-colitis). The protective dose of saffron (150 mg/kg) in this study was selected according to our previous work in which azoxymethane/DSS induced colitis-associated colorectal carcinogenesis model. The daily weight changes, colon macroscopic and microscopic histological changes were evaluated. **Result:** saffron (150 ppm) caused a significant reduction in "Colitis Index", "Inflammation Severity" and "Crypt damage severity"($p<0.001$) in both short term and long term treatment group and a significant differences were detected between these two group when compared with colitis group. **Conclusion:** Saffron may be considered as the treatment and preventive choice for Ulcerative Colitis.

Key word: Ulcerative colitis, Saffron, *Crocus Sativus L.*, Invivo model, Histopathology

BACKGROUND

Although pathogenesis of ulcerative colitis as one of the inflammatory bowel disease remain unclear but is a recurrent disease with varying degrees of the inflammatory process with extra intestinal manifestations(1). Nowadays,the therapeutic approach for inflammatory bowel disease treatment were focused on the use of anti-inflammatory oral medications(2, 3) because the amount of reactive oxygen species reactive oxygen species (ROS) and free radical (FR) are high in colonic cell of IBD patients when compared by normal physiological conditions, in which oxidative stress level is low(4). The results of the treatment with synthetic anti-inflammatory agent in some patients remain unsatisfactory (5-8). Therefore, the researchers are seeking new natural phytotherapeutic agents for treatment

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of IBD. There are many experimental colitis studies in which many medicinal plants and natural herb with antioxidants activity show beneficial effects (9, 10).Thus, using natural herb that have antioxidant properties with minimal adverse reactions during treatment is important.

Saffron might be such a potential candidate(11). *Crocus sativus* L., commonly known as saffron used in traditional medicine for treatment of various conditions (12-15). Saffron is the richest source of bioactive phytochemicals including carotenoids, flavonoids and several components derived from its carotenoids(16, 17).

Saffron's carotenoids display antioxidant, anti-inflammatory and anticarcinogenic activities(18-21). Saffron exerts its antiinflammatory effects(22) by the modulation of lipid peroxidation, cytokines, TNF-a, IL-1b, decreasing mucosal PGE2, IL-6 and MPO. Antioxidant effects of saffron(23, 24) lead to reduced MDA, and MPO, increment in GSH, and SOD activities and inhibition ROS-dependent MEK1/2 pathway.

Various animal models of experimental colitis screen the efficacy of natural herb usage against acetic acid-induced colitis which mimics some of the histology and acute inflammatory responses of human ulcerative colitis(25). In the current study, the modulatory effect of saffron in experimental model of ulcerative colitis induced by acetic acid was studies. This may be the first report describing the effect of saffron against ulcerative colitis in animal model. We also use the protective dose of saffron (150 mg/kg) in this study according to previous work we had done in azoxymethane induced colitis-associated colorectal carcinogenesis model

PROCEDURE

Plant material/Isolation of Saffron (Crocus Sativus L.) Stigma Extract

The part of saffron.that is being used as additive is the stigma. Dry stigmas of pure saffron were purchased from Golpeech Ltd.(St. Mash'had, Iran), and keep in a dark and cold (4°C) place. *Mash'had* the capital of *Khorasan razavi* province has mild and dry climate which has proper environment for saffron cultivation. Much of saffron in Iran is exported from this province. Saffron was identified by "the Pharmacological Research Center" of Medicinal Plants of School of Pharmacy with the herbarium code of (PM 832). Extraction of saffron's stigma were done in medicinal & natural products chemistry research center of Shiraz University of Medical Sciences. Dried stigmas of saffron were milled mechanically by mortar grinding machine. Light-color liquid extracts of saffron's stigma were obtained by soxhlet apparatus in which ethanol (80%) were used as a solvent. Ethanol was then removed by rotary evaporator in 42°C with vacuum pressure of 62 hPa (pascal/hour). The dark-red thick liquid extract were dried by freeze dryer in -42.5°C with vacuum pressure of 180 pascal.

Animals

Thirthy-two adult male Sprague-Dawley rats with an initial mean weight of 350 ± 20g were used. 8 rats were housed in each cage and maintained under a 12-hour light/dark cycle at a temperature of 22°C and relative humidity of 50% with access to standard rat chow pellets(*Behparvar* Company, Shiraz, Iran) (the nutritional composition of the pellets consisted of 88% dry matter, 14% crude protein, 10% crude ash, 11% crude cellulose, 1.3% to 2.0% calcium, 1% phosphorus, 1% NaCl, and 2.6 kcal/g) and ad libitum water. The experimental protocol of the present study was approved by the Ethics Committee on Animal Experimentation(26).

Experimental Induction of Colitis

Animals were fasted for 48 h and lightly anesthetized with diethyl ether. Colonic inflammation was induced by rectal administration of 2 ml acetic acid (4%). The rats were then held in an upside-down position for 2-3 min to avoid immediate anal leakage of the instillate. Thereafter, the rats were returned to their cages and had access to food and water *ad libitum*.

Animal Grouping

Animals were randomly allocated to different groups: colitis, saffron and the test (short term and long term) groups. For each group, eight rats were used. Colitis group was acetic acid induced colitis rats. The *saffron* groups were treated with doses of 150mg/kg for seven days. This dose were selected based on the previous study which we have done on Azoxymethane –induced colon carcinogenesis and we saw this dose was protective. The long term group was given the dose of 150 mg/kg saffron extract for 21days before induction of UC and were continued for another 6 consecutive days after UC was induced. The short term group was acetic acid induced-colitis rats treated with 150 ppm for 6 days.

All saffron treatments were started 2 h before induction of the colitis and continued daily for 6 consecutive days.

Microscopic (Histological) Studies

The colon was scored for microscopically visible damage by pathologist who were unaware of the study groups, according to the criteria described by Dieleman and colleagues(27)(Table 1), Onderdonk et al. (28) and Murthy et al. (29), which take into account the extent and the severity of colonic damage. "Total colitis index" was measured by summing three sub-scores "inflammation severity", "inflammation extent", and crypt damage. "crypt damage severity" was measure from multiplying

crypt damage to inflammation severity and " inflammation severity" was measure from multiplying inflammation extent to inflammation severity.

Total colitis index was measured by summing three sub-scores inflammation severity (0: None, 1: Mild, 2: Moderate: 3: Severe), inflammation extent (Onderdonk grading system(28)), and crypt damage (Murthy grading system(29)).

Statistical Analyses

Nonparametric data of colitis including macroscopic and histological scores were analyzed by Kruskal–Wallis H test and Mann–Whitney U test at 5% significance level. The *P* values of 0.05 and less were considered statistically significant. SPSS 19 software was used to analyze the data.

RESULT

Effect of oral administration of total stigma extract of extract of *saffron (Crocus Sativus L.)* on microscopic and histopathological parameters of the rat colon after induction of colitis with acetic acid (%4) are shown in Figure 1. Scores for tissue sections prepared for the microscopic examination was quantified as "colonic damage severity", "inflammation severity" and "total colitis index" as described in Table 1.

The total Colitis Index of colitis group was significantly the highest score(23.69) and the saffron group significantly showed a lower one(9.75) (P=0.016) (Table 2). Saffron significantly reduced total colitis index in short term and long term saffron treated-colitis groups (18.63 and 13.94 respectivelty) in comparison with the colitis group (P=0.016). (Table 2).

Long term usage of saffron total extract (after induction of ulcerative colitis) reduced total colitis index scores more than short term usage of saffron total extract(13.94 vs 18.93) (Table 2). Saffron could reduce "cryptal damage severity"- and "inflammation severity"- score in two saffron treated-colotis groups and trends of reduction is also as similar for total colitis index scores (Table 3 & 4). The pathological lesions and their qualitative grades are presented in Figure 1. As demonstrated, the protective dose saffron (150ppm) caused less microscopic changes in both saffron treated -colitis groups when compared with the colitis group.

There were no significant differences in the mean weight of the rats between different groups before the study and until the 7nd day of the study (P > 0.05). Only significant differences were detected between colitis group and "long term saffron usage-UC induction" group on the 1st (P= 0.017), 2nd (P=0.021), 3rd (P = 0.025) days.The

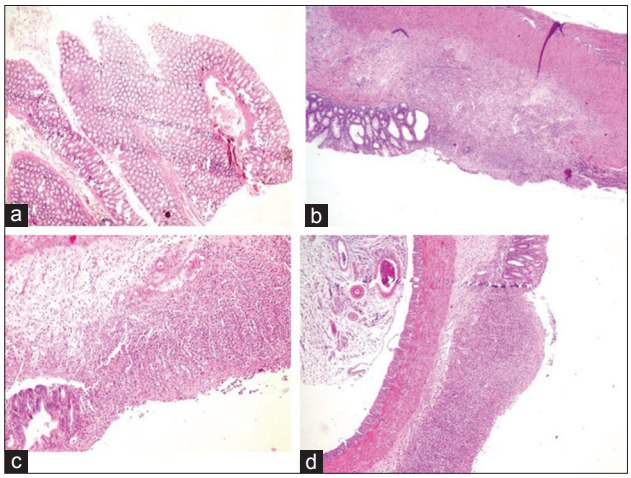

Figure 1: Microscopic presentation of acetic acid-induced colitis in rats treated by saffron (H&E staining; original magnification × 40). (Photographe was taken by a dual-head Olympus BX51 microscope). Each viewing field was categorized in to one of four histological categories: (a) normal, (b) mild-, (c) moderate- and (d) severe-destruction of epithelial crypt

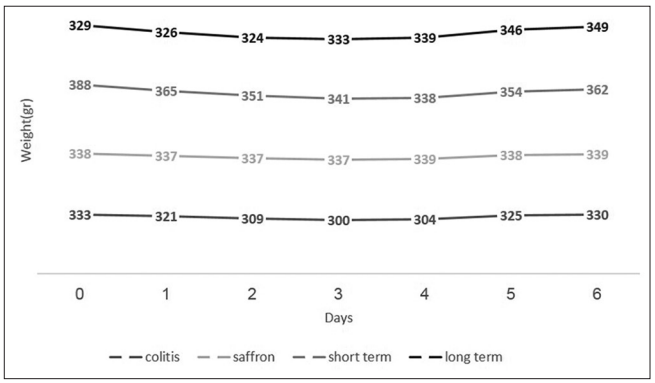

Figure 2: The weight changes of rats in different groups during the experimental period. Each value has been represented as Mean±SEM (n=8). Stars shows statistically significant difference in comparison with the colitis group (*P<0.05)

Table 1: Microscopic scoring system of changes in ulcerative colitis

Score	Crypt damage (Murthy)	Inflammation extent (Onderdonk)	Inflammation severity
0	Normal crypt	Normal	None
1	Destroying of the 1/3 of crypt	Local leucocytes infiltration	Mild
2	Destroying of the 2/3 of crypt	Leucocytes infiltration and crypt abscess	Moderate
3	Complete destroying of the crypt but normal epithelium	Mucosal lesion	Severe
4	Complete destroying of the crypt and epithelium	-	-

Table 2: Effect of saffron total extract on total colitis index of acid acetic-Induced ulcerative colitis in male rats

	Colitis[1]	Short term[2]	Long term[3]	Saffron[4]	P-value
Mean rank	23.69	18.63	13.94	9.75	0.016

1-Ulcerative colitis group was acetic acid induced colitis rats, 2- acetic acid induced-colitis rats treated with 150 ppm for 6 days, 3- acetic acid induced-colitis rats treated with 150 ppm for 30 days as describe in methos. 4- treated with doses of 150 ppm of total saffron extract for seven days

Table 3: Frequency of different histopathologic grades of crypt damage severity in the colon of rats subjected to ulcerative colitis

	None	Basal 1/3 damage	Basal 2/3 damage	Crypt damage surface epithelial present	Crypt lost surface epithelial lost	Mean rank	P-value
Colitis1	0	0	0	12.5	87.5	23.38	
Short term2	25	0	12.5	62.5	0	16.31	0.073
Long term3	37.5	25	0	25	12.5	14.25	
Saffron4	87.5	12.5	0	0	0	12.06	

1- Ulcerative colitis group was acetic acid induced colitis rats, 2- acetic acid induced-colitis rats treated with 150 ppm for 6 days, 3- acetic acid induced-colitis rats treated with 150 ppm for 30 days as describe in methos. 4- treated with doses of 150 ppm of total saffron extract for seven days,

Table 4: Frequency of different histopathologic grades of inflammation severity in the colon of rats subjected to ulcerative colitis

	None	Mild	Moderate	Severe	Mean rank	P_value
Colitis[1]	0	25	37.5	37.5	22.13	
Short term[2]	0	50.00	50.00	0	18.81	0.037
Long term[3]	37.5	25	37.5	0	15.56	
Saffron[4]	87.5	12.5	0	0	9.50	

1- Ulcerative Colitis group was acetic acid induced colitis rats, 2- acetic acid induced-colitis rats treated with 150 ppm for 6 days, 3- acetic acid induced-colitis rats treated with 150 ppm for 30 days as describe in methos. 4- treated with doses of 150 ppm of total saffron extract for seven days,

changes in the mean weight of the rats before and during the experimental period are presented in Figure 2.

DISCUSSION

The present investigation showed that saffron extract has protective effect against experimental ulcerative colitis and this effect were more significant when long term usage of saffron were consumed because the levels of colonic index score, inflammation severity and crypt damage severity were reduced.

According to current results, the changes in the mean weight of the rats during the experimental period showed a significant reduction till day 3 and the variation in weight change was less in saffron-treated groups rather than colitis group. Ulcerative colitis lead to an inflammation of colon cells. The inflammation lead to ulceration and disturb the proper absorption of water and nutrients into the circulation, and lead to bleeding and other nutrient related problems which affect body weight. In IBD, oxidative stress plays a role in disease initiation and progression(30).

epithelial cell integrity and mucosal recovery of colonocytes were disrupted by free radicals and ROS, especially in case of impaired endogenous defense systems(31). Saffron is as one of the plants with highest carotenoids content with high antioxidant values (24, 32-34). Thus their ability to inhibit free radical generation offers another explanation of the anti ulcerogenic activity of this plant. Beside its anti-inflammatory and antioxidant effect, its anticarcinogenic action (35-38) may add to its beneficial effect; because patients with inflammatory bowel diseases (IBD) are at high risk of developing CRC. It is worthy to mentioned that Kazi and colleagues(20) studied anti-inflammatory effect of crocetin- one of the active carotenoids of saffron- in ulcerative colitis model which induced by 2, 4, 6- trinitrobenzene sulfonic acid (TNBS). Their study showed that crocetin have protective effect. Although our method in colitis induction was by acetetic acid, but our results were in accordance with Kazi et al study. We also used saffron total extract rather than one or some separate carotenoids, because total extract may exert different way of action and the mechanism of action of each carotenoid in saffron related to concentration of other carotenoids(39).

Findings of the present investigation may promise protective results in other models of ulcerative colitis in future, in which saffron's extract may trigger some biochemical biomarkers like as lipid peroxides (LPOs) and protein carbonyls (PCOs) levels which indicate ROS formation, the activity antioxidant enzymes (SOD, CAT and GPX) and GSH levels, myeloperoxidase(MPO) as indication of "in filtered neutrophil"(40) and also cytokines which playing a central role in inflammation.

CONCLUSION

Ulcerative Colitis is currently treated with synthetic drug, but our findings suggest long term usage of protective dose of saffron extract(150 ppm) may be as a new therapeutic approach because a significant reduction in "colitis index", "inflammation severity" and "crypt damage severity" were

seen based on histopathology evaluation. Further studies should be done to clarify this fact.

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