Ann Colorectal Res. 2016 June; 4(2):e37285. doi: 10.17795/acr-37285.

Published online 2016 June 18. **Research Article**

Oral Grapeseed Oil and Sesame Oil in Experimental Acetic Acid-Induced Ulcerative Colitis in Rat

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Received 2016 February 20; **Revised** 2016 May 16; **Accepted** 2016 June 12.

Abstract

Background: Ulcerative colitis (UC) is a multi-factorial disease with unknown etiology and has many clinical manifestations.
Objectives: The current study aimed to evaluate the effects of sesame oil (SO) and grapeseed oil (GSO) on acetic acid-induced UC in rats.
Materials and Methods: Eighty male rats were divided into eight groups as health control (HC_1), received normal saline; HC_2, received SO; HC_3, received GSO; negative control (NC), UC and normal saline; positive control (PC), UC and mesalamine; SO, UC and SO; GSO, UC and GSO, and SO + GSO. The daily weight changes, serum levels of oxidative stress markers and lipid profile plus colon macroscopic and microscopic histological changes were measured at the end of the seventh day.
Results: Significant differences were detected between HC_1 and PC on the 3rd ($P = 0.002$), 4th (0.013) and 6th days (0.014) and between HC_1 and NC on the 4th day (0.027) in weight of rats. Use of GSO alone or in combination with SO decreased the extent of the changes both in macroscopic and microscopic indices and also at the inflammation level. The most significant decrease in the MDA level and the most obvious increase in the TAC belonged to the GSO group in comparison to the NC group. The lowest cholesterol (51.43 ± 5.62 mg/dL) and HDL levels (29.29 ± 6.24 mg/dL) were detected in response to SO consumption in comparison to NC group ($P = 0.030$ and $P = 0.257$, respectively).
Conclusions: GSO in combination with SO may be considered as the treatment of choice for UC based on antioxidant and histopathological evaluations.

Keywords: Grapeseed Oil, Sesame Oil, Ulcerative Colitis, Oxidative Stress, Histopathology

1. Background

Ulcerative colitis (UC) along with the Crohn disease (CD) are two types of inflammatory bowel disease (IBD) defined as relapsing, chronic and remitting inflammatory diseases of the large intestine (1). UC is a complex and multi-factorial disease with unknown etiology caused by several pathophysiological mechanisms and many clinical manifestations (2, 3) including diarrhea, abdominal or rectal pain, fever, weight loss and blood in the stool (4). There are several strategies such as medical and surgical therapies to treat UC, but surgery is indicated for the cases unresponsive to medical therapy. The extent and severity of UC and its anatomic location affects agents used to induce remission in patients with UC, including both oral and topical regimens. Sulfasalazine and its aminosalicylate analogues, corticosteroids, immunomodulators, suppressive antimetabolites, anti-tumor necrosis factor-biologics including infliximab, and in some cases antibiotics are reported as treatments of choice (5).

However, it is reported that some dietary behaviors such as animal protein and lipid intake and inadequate use of vegetable and plant based food can be the risk factors for the development of UC (6, 7). In addition, use of new treatment strategies such as using medicinal plants and their derivatives including oil, extracts and active substances are more popular. Grape seed oil (GSO) is rich in unsaturated fatty acids (more than 89% of the total oil composition) and antioxidants such as tocopherols and phytosterol (8). Sesame oil (SO) has antioxidant, anti-inflammatory, and antibacterial properties (9). This oil also contains various lignans such as sesamin and

sesaminol that prevent the release of proinflammatory agents, which ultimately prevent inflammation (10).

Although there was a report on using SO to treat UC (11), there were no previous reports on using GSO, or its combination with SO to treat UC in human or animal models.

2. Objectives

The current study aimed to evaluate the healing effects of GSO and SO as dietary dosage and compare them with mesalamin in male rats with experimentally acetic acid-induced ulcerative colitis. The study focused on the gross, macroscopic, microscopic, oxidative and biochemical changes of UC and their alterations in response to both treatments in oral dietary application. In addition the serum lipid profile was evaluated because these two oils are one of the items in male food basket. If these two plant based oils had the beneficial effects on the treatment of UC, and just after performing randomized control trial, they can advised as a part of daily food consumption in all people, especially the ones with UC in their families as an preventive dietary therapy.

3. Materials and Methods

3.1. Oil Sources

Zareentalia Grapseed oil 1 Liter (Zareentalia Co., Italy) and Samar sesame oil (Samar Co., Iran) were used in the study. These two products were prepared from the best quality raw materials and had the standard production certificates.

3.2. Animals, Housing, UC Induction and Treatments

Eighty male Sprague Dawley rats weighing 200 $\pm$ 20 g were provided from the center of experimental and comparative medicine, Shiraz University of Medical Sciences, Shiraz, Iran. The rats were randomly allocated into eight equal separated groups according to Table 1. The rats were housed in standard cages under 12/12 light-dark schedule (lights on at 7:00 pm) with an ambient temperature of 22 $\pm$ 2°C, and 55% relative humidity.

Animals were off fed for 36 hours before induction of UC to empty the colon. UC was induced according to the previously reported protocols (12). All animals were fasted overnight and their bowels were cleaned before induction of UC. A polyurethane cannula (2 mm diameter) was applied for the rectal entrance of acetic acid and 2 mL of 3% acetic acid was administered transrectally into the colon to induce UC under ketamine-zaylazine anesthesia. Treatment with normal saline, mesalamine, GSO and SO were applied to desired groups for seven days after UC induction according to Table 1. The weight changes were recorded during the seven days by using digital scale with 0.1 g precision.

3.3. Macroscopic Evaluations

At the end of the seventh days, the rats were sacrificed in the CO_2 induction box. Then, the distal 8 cm of the colon was removed and dissected by longitudinal incision. The mucosal injury was macroscopically assessed using grading scale reported previously (13) and reported as scores 0 - 5.

3.4. Microscopic Evaluations

Colon tissue was processed and stained according to the previously reported procedures (14-16). All sections were studied and photographed using a light microscope. The degree of inflammation of the colon was graded as 0 - 3 according to the previous report by Onderdonk et al. (17). Also, the crypt injury was graded as 0 - 4 based on the report by Murthy et al. (18). The means of each score in each grading system is presented in Table 2.

3.5. Oxidative Stress Evaluation

The blood sample was taken from the heart of each rat in each group. The serum was separated using centrifugation (3000 rpm, 10 minutes) and then stored in -70°C. The malondialdehyde (MDA) level, as the end-products of lipid peroxidation (LPO), was assessed via the measurement of thiobarbituric acid reactive substances (TBARS) in sera (19). The determination of total antioxidant capacity (TAC) in serum was performed by colorimetric method using commercial kit (Cayman, USA).

3.6. Inflammation Indices and Lipid Profile Measurements

The serum level of IL-6 was measured using rat specific sandwich enzyme-linked immunosorbent assay (ELISA) kit (Sigma Aldrich, USA). Serum C-reactive protein (CRP) samples were evaluated by enzyme immunoassay kit (IBL international, Germany). Cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) were measured by colorimetric method using commercial kits (ParsAzmoon Co., Iran) and biochemical Autoanalyzer (BT-1500, Italy).

3.7. Statistical Analysis

The data were presented as mean and standard deviation. Normal distributions of the data were assessed by Kolmogorov-Smirnov test. One-way ANOVA and Tukey post hoc test were used to compare the mean differences in all variables between the eight groups. $P < 0.05$ was considered statistically significant. Mann-Whitney U

Table 1. Experimental Grouping and Treatments

Group No.	Abbreviations	UC Induction	Normal Saline (4 mL/kg)	Mesalamine (100 mg/kg)	GSO (4 mL/kg)	SO (4 mL/kg)
1	HC_1	-	+	-	-	-
2	HC_2	-	-	-	-	+
3	HC_3	-	-	-	+	-
4	NC	+	+	-	-	-
5	PC	+	-	+	-	-
6	SO	+	-	-	-	+
7	GSO	+	-	-	+	-
8	SO + GSO	+	-	-	+	+

Abbreviations: GSO, grapeseed oil; HC, health control; NC, negative control; PC, positive control; SO, sesame oil; UC, ulcerative colitis.

Table 2. Macroscopic and Microscopic Grading System of Changes in Ulcerative Colitis

Score	Morris	Murthy	Onderdonk
0	Without damages	Normal crypt	Normal
1	Local congestion without lesion	Destroying of the 1/3 of crypt	Local leucocytes infiltration
2	Linear lesions without severe inflammation	Destroying of the 2/3 of crypt	Leucocytes infiltration and crypt abscess
3	Linear lesions with focal inflammation	Complete destroying of the crypt but normal epithelium	Mucosal lesion
4	Lesion or inflammation in more than two points	Complete destroying of the crypt and epithelium	-
5	Score 4 which affected more than one cm of colon	-	-

test and Bonferroni correction were used to compare the histopathology scores between different groups on different days. SPSS 16.5 software was used to analyze the data.

4. Results

The changes in the mean weight of the rats before the experiment and during the seven days of experimental period are presented in Figure 1. There were no significant differences in the mean weight of the rats between different groups before the study and until the 2nd day of the study ($P > 0.05$). Only significant differences were detected between HC_1 and PC on the 3rd ($P = 0.002$), 4th (0.013) and 6th days (0.014) and HC_1 and NC on the 4th day (0.027).

The pathological lesions and their grades are presented in Figure 2. Also, the results of macroscopic and microscopic evaluations of the changes in the colon tissue are presented in Table 3. As demonstrated, UC caused more macroscopic and microscopic changes plus more inflammation in the colon compared with the control group. Use of GSO alone or in combination with SO decreased the extent of the changes both in macroscopic and microscopic indices and also at inflammation level. However, use of SO alone cannot significantly affect these pathological features and all indices were significantly higher than those of the health control group ($P < 0.05$).

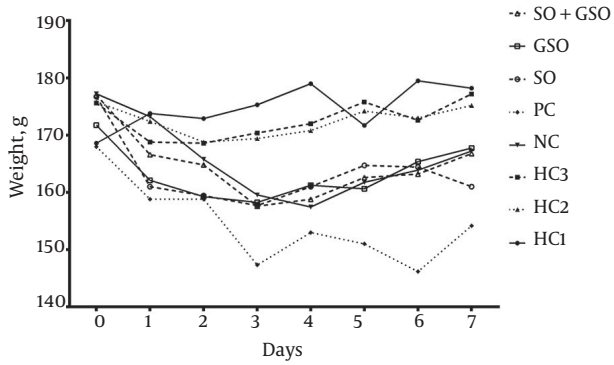


Figure 1. The Weight Changes of Rats in Different Groups Before and During the Experimental Period

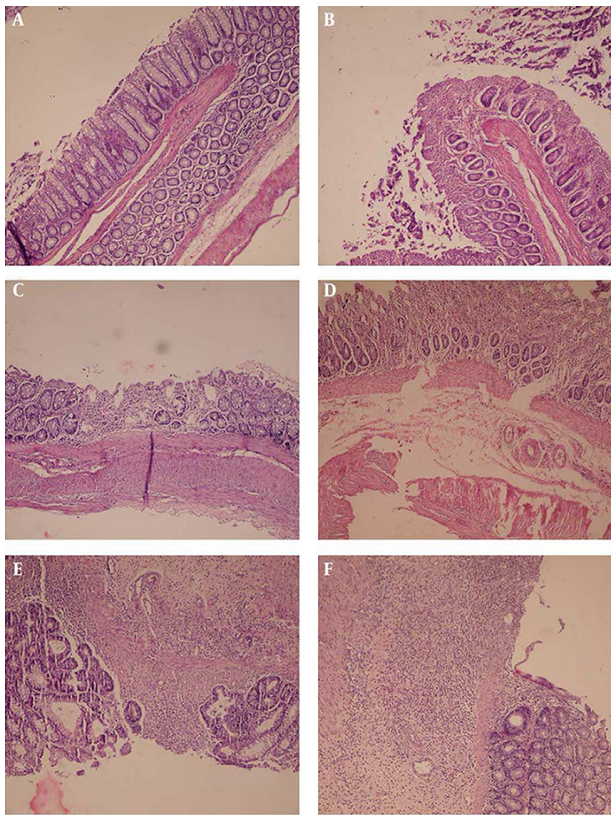
The results of oxidative stress indices, inflammation markers and lipid profile measurements are presented in Figure 3. No significant differences were detected in the CRP, triglyceride and LDL level between different groups. The highest MDA level (9.81 ± 1.43 μM/L) and lowest TAC (1.29 ± 0.48 mM/L) belonged to the NC group in which the

Table 3. Macroscopic (Morris) and Microscopic (Onderdonk and Murthy) Evaluations of the Colon Tissue in Different Groups[a, b]

Groups	Morris	Onderdonk	Murthy
HC_1	0.00 ± 0.00^{a}	0.00 ± 0.00^{a}	0.00 ± 0.00^{a}
HC_2	0.20 ± 0.45^{a}	0.40 ± 0.89^{a}	0.20 ± 0.45^{a}
HC_3	0.20 ± 0.45^{a}	0.00 ± 0.00^{a}	0.00 ± 0.00^{a}
NC	3.00 ± 1.32^{b}	2.67 ± 0.87^{b}	2.44 ± 0.53^{b}
PC	0.67 ± 0.82^{a}	0.17 ± 0.41^{a}	0.17 ± 0.41^{a}
SO	3.14 ± 1.07^{b}	2.43 ± 1.72^{bc}	1.86 ± 1.21^{bc}
GSO	0.88 ± 0.99^{a}	0.38 ± 0.74^{a}	0.38 ± 0.74^{a}
SO + GSO	0.60 ± 0.55^{a}	0.80 ± 1.30^{ac}	0.80 ± 1.30^{ac}

Abbreviations: GSO, grape seed oil; HC, health control; NC, negative control; PC, positive control; SO, sesame oil.
[a] Treatment in each group was conducted according to the Table 1.
[b] Significant differences in each column are demonstrated by different superscript letters ($P < 0.05$).

Figure 2. Pathological Lesions and Their Grades in Different Groups



From lower to higher grades, destroying of epithelial cells and replacing of functional cells by connective tissue are observed; A, grade 0; B, grade 1; C, grade 2; D, grade 3; E, between grade 3 and grade 4; F, grade 4

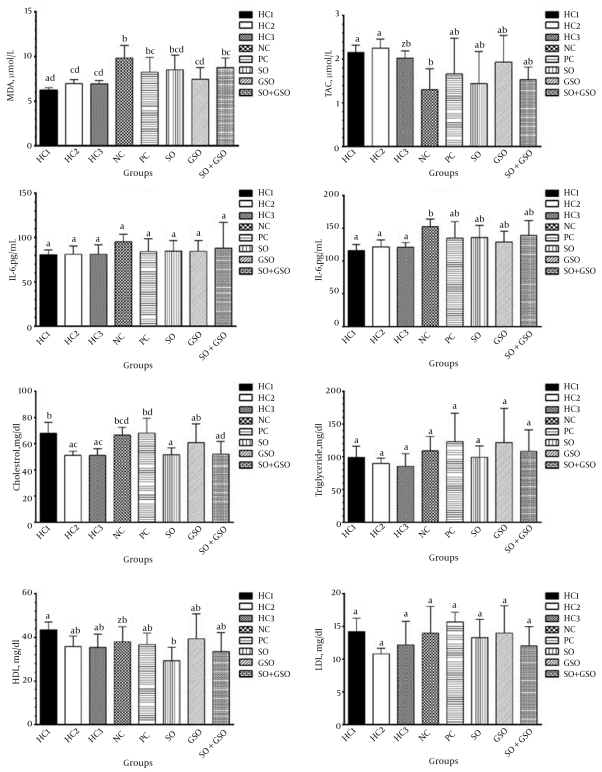
rats had UC but used no treatments. Also, the highest level of IL-6 (152.55 ± 11.42 pg/mL) was detected in the group. The most significant decrease in the MDA level (7.43 ± 1.33 μM/L vs. 9.81 ± 1.43 μM/L, P = 0.003) and the most obvious increase in the TAC (1.93 ± 0.61 mM/L vs. 1.29 ± 0.48 mM/L, P = 0.220) between the three treatment groups (SO, GSO, and SO + GSO) belonged to the GSO group in compassion to the NC group. Finally, the lowest cholesterol (51.43 ± 5.62 mg/dL) and HDL levels (29.29 ± 6.24 mg/dL) were detected in SO consumption group compared with the NC group (P = 0.030 and P = 0.257, respectively).

5. Discussion

In the present study, the healing effects of GSO alone or in combination with SO were evaluated in the experimental induced UC in rats. Also, the oxidative stress indices, inflammation markers and lipid profile changes were measured in response to different treatments. It was found that oral combination of GSO and SO had better healing effects in comparison to each treatment alone, based on macroscopic and microscopic indices and also inflammation level. However, administration of oral GSO and oral SO, each in therapeutic or dietary applications alone, was most applicable and had more efficacies in antioxidant and lipid profile changes, respectively. In addition, their beneficial effects on the lipid profile suggested that GSO and SO can be considered as a dietary regimen in patients with UC.

UC, as a form of IBD, is a major health problem and a persistent UC can increase the risk of colorectal cancer development by ~10 folds (20). Therefore, effective treatments in appropriate time are necessary to prevent and/or treat the disease. Several therapeutic agents are reported to treat UC including sulfasalazine and its aminosalicylate analogues, corticosteroids, immunomodulators, suppres-

Figure 3. Oxidative Stress Indices, Inflammation Markers and Lipid Profile Changes in Different Groups After Seven Days of Treatment



GSO, grape seed oil; HC, health control; NC, negative control; PC, positive control; SO, sesame oil; treatment in each group was conducted according to the Table 1. Significant differences between groups in each variable are demonstrated by different superscript letters ($P < 0.05$).

sive antimetabolites, antitumor necrosis factors such as infliximab, and in some cases antibiotics (5). In recent years use of herbal medicine to treat approximately all diseases of human and also animal models has clearly increased. For instance, there were some reports on using *Teucrium polium* (5) and *Calendula officinalis* (21) in dog and licorice (22), strawberry (23), *Pistacia atlantica* (24), *Hypericum perforatum* (1) and *Berberis vulgais* (25) in rats. To the authors' best knowledge, no paper is published on the effects of GSO and its combination with SO to prevent or treat UC, in man or animals. There was only one report on using SO to heal acute colitis. It concluded that using 4 mL/kg for seven days, similar to the current study, attenuated 2,4,6-trinitrobenzenesulfonic acid-induced acute colitis in rats by inhibiting inflammation, acidic mucin, and fibrosis (11). In addition, it is reported that GSO increased serum HDL levels and reduced LDL levels in healthy people (26). Also, the current study demonstrated similar changes in both LDL and HDL levels in the GSO group compared with those of the NC group.

SO is a derived from *Sesamum indicum* L., a herbaceous annual belonging to the Pedaliaceae family. This oil contains olein, stearin, palmitin, myristin, linolein, sesamin and sesamolin (27). It is reported that using SO increases the hepatic detoxification of chemicals and protects against oxidative stress (28). Also protection against endotoxemia or sepsis by daily consumption of SO is possible due to its antioxidant components (29, 30). As an adjuvant, SO may offer an additional effect to other drugs via its potent anti-oxidative effects (31). Also, GSO contains some antioxidants such as tocopherols, which is of interest to the pharmaceutical field due to its potential beneficial effects on human and animal health (32). Although the current study found some beneficial effects and antioxidant properties of the GSO, the cold-pressed GSO contains negligible amounts due to its insolubility in lipid (33). Therefore, antioxidant contents of this oil must be evaluated using special analysis techniques. Only SO usage produced some changes in lipid profile which had no significant patterns. However, consumption of GSO alone or concurrent use of SO and GSO produced significant clear antioxidant and healing effects. It seems that GSO has some constituents which show such beneficial therapeutic and dietary effects.

Despite the current study findings, the present study had three major limitations. First, another group should be defined as HC_4 in which the mixture of GSO and SO is used in healthy rats to find any unwanted interactions between them. Second, both oils should have been analyzed by gas chromatography mass spectroscopy (GC-MS) to find their contents and possible potential constituents. Finally, the number of rats in each group can be higher than that of the current study to help the judgment about the findings and their significance.

5.1. Conclusion

The study showed that daily oral consumption of grapeseed oil and sesame oil can relieve the ulcerative colitis induced by acetic acid in rat colon. Results of serum oxidative markers, inflammatory indices and lipid profile and also histopathological evaluations indicated a reduction in inflammation. The healing and anti-inflammatory properties of both oils can make them as appropriate dietary regimen and/ or drug choice to treat ulcerative colitis. Further studies are required to confirm the clinical effectiveness in humans.

Acknowledgments

The present article was extracted from the Ph.D. thesis (ID: 7167) of Fatemeh Hosseinzadeh and was financially

supported by the Shiraz University of Medical Sciences, Shiraz, Iran.

Footnote

Authors' Contribution: Moosa Salehi and Nader Tanideh played the same role in this article and both were corresponding author; Fatemeh Hosseinzadeh, acquisition of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content; Nader Tanideh, study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical and material support and study supervision; Negar Azarpira and Azadeh Sayarifard, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content; Masood Sepehrimanesh, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis; Moosa Salehi, study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical and material support and study supervision.

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