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Original Article

Evaluation of Anti-inflammatory and Antioxidant Profile of Oleuropein in Experimentally Induced Ulcerative Colitis

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Oleuropein is one of the main phenolic secoiridoid of the olive leaf extract, which is known for its antioxidant and anti-inflammatory effects. The main objective of the present study was to investigate the effectiveness of oleuropein in the ulcerative colitis treatment. An experimental study was designed on rats, which were divided into three groups, group 1 (normal control), group 2 (induced for ulcerative colitis and untreated), and group 3 (induced for ulcerative colitis and treated with oleuropein). Colonic tissue samples were collected from all studied groups and the oxidative stress and antioxidant activity were assessed by evaluating malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), myeloperoxidase (MPO), and nitric oxide (NO) levels. The expression levels of pro-inflammatory cytokines such as *IL-1β*, *TNF-α*, *IL-10*, *COX-2*, *iNOS*, *TGF-β1*, *MCP-1*, and *NF-κB*, the pro-apoptotic gene *Bax*, and the anti-apoptotic gene *Bcl2* were assessed in colon tissues to evaluate the effectiveness of oleuropein treatment. Oleuropein was effective on reducing the mortality rate and disease activity index. Oleuropein caused a significant reduction in colon MDA, MPO, and NO levels and a significant elevation in SOD, CAT, and GPX levels and induced the down regulation of analyzed proinflammatory cytokines. Also, downregulation of *Bax* and upregulation of *Bcl2* were observed as a result of oleuropein treatment in comparison with untreated acetic acid induced ulcerative colitis group. Oleuropein showed intestinal anti-inflammatory, antioxidant, and anti-apoptotic effects in ulcerative colitis experimental model.

Key words: Ulcerative colitis, oleuropein, anti-inflammatory, antioxidant, *Bax*, *Bcl2*

Inflammatory bowel disease (IBD) is a group of long- lasting disorders categorized into two major types: ulcerative colitis (UC) and Crohn's disease, characterized by a recurrent idiopathic inflammation and linked with immune system dysregulation (1, 2). The etiology of IBD especially

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UC is associated with both genetic and environmental factors with not fully understood pathogenesis (3, 4). Ulcerative colitis (UC) affects the large intestine (colon) and rectum; the most common disease symptoms include abdominal pain, bloody diarrhea, weight loss, fever, and anemia. The main complications of this disease include megacolon, colon cancer, and extra-intestinal complications such as osteoarticular and skin involvement (2, 5). Oxidative stress is one of the main participating factors involved in the disease complication and development. Oxidative stress results from either reactive oxygen species (ROS) overproduction or a decreased antioxidant activity (6, 7). The antioxidant system comprises enzymes such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), myeloperoxidase (MPO), catalase (CAT), and nitric oxide (NO) (8). UC is associated with the release of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and nuclear factor (NF)-κB (9). The available treatments for UC include aminosalicylates, corticosteroids, immunosuppressants, and antibiotics (10). Recently, botanical drugs have shown a distinguished safe effect through modulating the inflammatory response (11). *Olea europaea L.* is one of the most common available botanical drugs; olive leaf extracts have several effects including antihypertensive, antiatherogenic, anti-inflammatory, hypoglycemic, and hypocholesterolemic activities (12). The olive leaf extracts contain several bioactive compounds, especially phenolic compounds such as phenolic acids, phenolic alcohols, flavonoids and secoiridoids (oleuropein) (13). Oleuropein has an antioxidant effect; it reduces the levels of ROS in pressure ulcers (14). Oleuropein also has anti-inflammatory effect, due to its ability to inhibit pro-inflammatory cytokines synthesis (15, 16). The primary objectives of the present study are to evaluate the effect of oleuropein olive leaf extract in UC treatment by measuring antioxidative stress and antioxidant activity including (MDA, MPO, NO, SOD, CAT, and GPX) in colonic tissue of the rats. Secondly we also aimed to perform a molecular analysis of pro-inflammatory cytokines such as (*IL-1β*, *TNF-α*, *Il-10*, *COX-2*, *iNOS*, *TGF-β1*, *MCP-1*, and *NF-κB*) in addition to the pro-apoptotic gene *Bax* and the anti-apoptotic gene *Bcl2* in colonic tissues.

Materials and methods

The study groups

Male laboratory albino rats (n = 30) of similar weight (6-8 weeks old) were purchased from the animal house of the Faculty of Veterinary Medicine, Kafr Al-shiekh University, Egypt. All rats were kept in specific pathogen free cages maintained on standard clean rodent food and tap water ad libitium. All procedures of the present study were conducted in accordance with the Institutional Animal Ethics Committee, Kafr Al-shiekh University guidelines. Study period for all groups was 1 week. Rats were divided into three groups which include 10 rats each. Group 1 (normal control); group 2 (positive control) received 2 ml intrarectal acetic acid 4% to induce colitis according to Kojima et al. (17). Briefly, rats were anaesthetized and a medical polyurethane canal was inserted into their anus up to 6 cm, and 2 ml of 4% acetic acid (Sigma Chemical Co. Egypt) was introduced into the colon. Group 3 (treated with oleuropein after 1 h acetic acid administration) received HPLC oleuropein 70% (Phytochem science Inc., China) at a dose of 350 mg/kg diluted in 1 ml normal saline. Oleuropein was given orally for 7 successive days. All groups were sacrificed after 1 week.

Biochemical analyses

The homogenized colon supernatants were used to determine the levels of the lipid peroxidation biomarkers MDA, SOD, CAT, GPX, MPO, and NO according to the manufactures'

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instructions (Bio-Diagnostics Co, Egypt). All biochemical parameters were determined spectrophotometrically on their specific wavelength (18).

RNA extraction and molecular analyses

Total RNA was extracted from the colonic tissue samples using RNA extraction kit (Qiagen, Valencia, CA, USA, cat. No, 74704) according to the manufacturers' instructions. RNA purity and quantity were determined by Q5000 137 nanodrop (Quawell, USA). Reverse transcription was conducted to synthesize the complementary DNA (cDNA) using Reverse Transcription kit (Qiagen, Valencia, CA, USA, Cat. No, 218161) according to the manufacturer's instructions. The total reaction volume was 20 µL containing 100 ng of the total RNA. qPCR was conducted for pro inflammatory cytokines such as (IL-1β, TNF-α, IL-10, Cox2, iNOS, TGF-β1, MCP-1, and NF-κB), and apoptotic genes (Bax, Bcl2). β- actin was the reference housekeeping gene. Specific primers were designed (Table 1) and used via Maxima SYBR Green/ROX qPCR Master Mix (Thermo Scientific, USA) in a StepOnePlus real time thermal cycler (Applied Biosystems, Life technology, USA). The PCR was performed according to the following conditions (95 ˚C for 15 s, 60 ˚C for 30 s, 72 ˚C for 30 s) for 40 cycles after initial denaturation (95 ˚C, 10 min). The critical threshold (Ct) values of target genes were normalized according to the formula $x = 2^{-\Delta\Delta Ct}$, where x = fold change relative to control.

Disease activity index (DAI) and mortality rate

The main clinical signs of UC were determined by evaluating the disease activity index (DAI) including stool consistency, rectal hemorrhage, and body weight loss (summarized in Table 2). DAI in all groups was observed daily after induction of colitis by acetic acid. The normal control group (G1) and the treated group with oleuropein (G3) showed no mortality during the whole experiment period. While, positive control group (G2) showed 20% mortality rate (two rats died of the overall 10 rats).

Statistical analysis

Table 1. Specific primer sequences used for real-time PCR.

Primer name	Forward (5′- 3′)	Reverse (5′- 3′)
TNF-α	ATGAGCACAGAAAGCATGA	AGTAGACAGAAGAGCGTGGT
IL-1β	TCCAGGATGAGGACATGAGCAC	GAACGTCACACACCAGCAGGTTA
COX-2	CCC CAT TAG CAG CCA GTT	CAT TCC CCA CGG TTT TGA
iNOS	GTT CTC AGC CCA ACA ATA CAA GA	GTG GAC GGG TCG ATG TCA C
IL-10	ATAACTGCACCCACTTCCCA	GGGCATCACTTCTACCAGGT
MCP-1	GCTCAGCCAGATGCAGTTAA	TCTTGAGCTTGGTGACAAAAACT
TGF-β1	CCTGCAAGACCATCGACATG	TGTTGTACAAAGCGAGCACC
NF-κB	GTGGTGCCTCACTGCTAACT	GGATGCACTTCAGCTTCTGT
β-actin	AAGTCCCTCACCCTCCCAAAAG	AGCAATGCTGTCACCTTCCC
Bax	CCTGTGCACCAAGGTGCCGGAACT	CCACCCTGGTCTTGGATCCAGCCC
Bcl-2	TGTGGCCTTCTTTGAGTTCGGTG	GGTGCCGGTTCAGGTACTCAGTCA

Table 2. Disease activity index (DAI) score.

Score	Weight loss %	Stool consistency	Occult/gross bleeding
0	0	Normal	Normal
1	1-5%	-	-
2	5-10%	Loose stools	Occult blood
3	10-15%	-	-
4	>20%	Diarrhea	Gross bleeding+ mucous

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Table 3. Effect of oleuropein on disease activity index (DAI) of experimental colitis.

	G1	G2	G3
Initial weight(g)	123.4 ± 4.2	124.3 ± 3.8	124.7 ± 3.9
Induction weight (g)	164.5 ±10.61	163.1 ±10.2	165.0 ± 9.8
Final weight (g)	165.9 ± 9.83	144.8 ± 8.90	154.8 ± 7.6
Body weight Score	0 ± 0	3.6 ± 0.12	2.1 ± 0.10
Stool score	0 ± 0	2.5 ± 0.13	2.3 ± 0.14
Blood score	0 ± 0	2.4 ± 0.17	1.0 ± 0.08
Disease activity index	0 ± 0	2.94± 0.16 [a]	1.46 ± 0.11 [b]

G1: normal control group; G2: acetic acid-induced colitis group; G3: oleuropein treated group. Data were statistically analyzed as mean ± SEM. Rows carrying different superscript letters [a (highest) – b (lowest)] are significantly different at $P \leq 0.05$.

Table 4. Colon weight and length in all study groups.

	Colon weight (g)	Colon length (cm)
	Mean± SEM	Mean± SEM
G1	1.06 ± 0.06 [b]	13.95 ± 0.72 [a]
G2	1.82 ± 0.09 [a]	8.73 ± 0.67 [b]
G3	1.19 ± 0.07 [b]	14.10 ± 0.73 [a]

G1: normal control group; G2: acetic acid-induced colitis group; G3: oleuropein treated group. Mean values with different superscript letters [a (highest) – b (lowest)] in the same column are significantly different at ($P \leq 0.05$). Data are presented as (Mean ± SEM); SEM = standard error of mean.

The results were expressed as mean ± standard error of mean (SEM). Data were statistically analyzed by One-way ANOVA followed by Dunnett's multiple comparisons test using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA. Statistical significance was set at $P \leq 0.05$.

Results

Evaluation of treatment with oleuropein on disease activity index (DAI)

The effect of oleuropein on DAI of experimentally induced colitis is summarized in Table 3. The obtained data exhibited a significant increase in DAI in acetic acid-induced colitis group (G2) in comparison with the normal control group (G1) ($P \leq 0.05$). The treated group with oleuropein (G3) showed significant reduction in DAI score ($P \leq 0.05$).

Colon weight and length

Table 4 shows the effect of oleuropein on colon weight and length. The obtained results showed a significant ($P \leq 0.05$) increase in weight and a decrease in length in acetic acid group (G2) as compared to the normal control group (G1). This increased weight was significantly reduced following the administration of oleuropein (G3). No significant difference was noticed between G1 and G3 (Figure 1).

Oxidative stress and antioxidant activity

Administration of acetic acid (G2) resulted in a significant elevation ($P \leq 0.05$) in colon MDA, MPO, and NO levels and a significant decline ($P \leq 0.05$) in colon SOD, CAT, and GPX levels in comparison with the normal control group (G1) (Table 5). In contrast, administration of oleuropein (G3) resulted in a significant reduction ($P \leq 0.05$) in colon MDA, MPO, and NO levels and a significant elevation ($P \leq 0.05$) in SOD, CAT, and GPX levels. The treatment did not return the disrupted oxidant/antioxidant parameter level to the normal level as noticed in G1.

Oleuropein effect on the relative expression of pro-inflammatory cytokines

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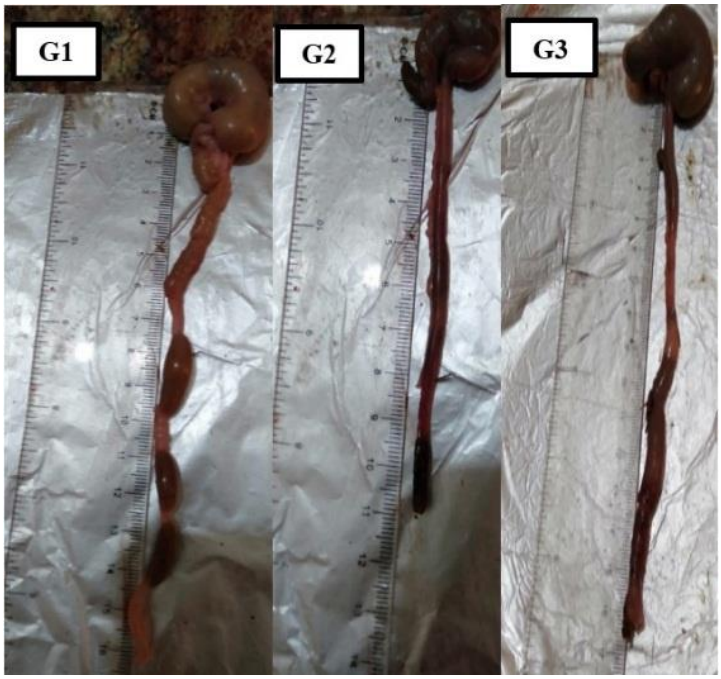


Fig. 1. Colon length in cm for all groups. G1: normal control group; G2: acetic acid induced group; G3: treated with oleuropein; x1.

Table 5. The Levels of MDA, MPO, SOD, CAT, GPX, and NO in colon tissues.

	Malondial dehyde nmol/g tissue	Myeloperoxidase U/mg tissue	Superoxide Dismutase U/g tissue	Catalase U/g tissue	Glutathione Peroxidase U/g tissue	Nitric Oxide mol/g tissue
	Mean± SEM	Mean± SEM	Mean± SEM	Mean± SEM	Mean± SEM	Mean± SEM
G1	0.17± 0.02 [c]	0.07± 0.005 [c]	6.27± 0.36 [a]	0.14± 0.01 [a]	0.14± 0.01 [a]	26.14± 1.2 [c]
G2	0.94±0.06 [a]	0.59±0.020 [a]	2.29±0.13 [c]	0.07±0.003 [c]	0.07±0.003 [c]	59.33±2.81 [a]
G3	0.49±0.04 [b]	0.24±0.010 [b]	3.81±0.19 [b]	0.1±0.005 [b]	0.1±0.005 [b]	40.18±1.6 [b]

G1: normal control group; G2: acetic acid-induced colitis group; G3: oleuropein treated group. Mean values with different superscript letters [a (highest) – c (lowest)] in the same column are significantly different at (P≤0.05). Data are presented as (Mean ± SEM); SEM = standard error of mean.

The qPCR data revealed a significant (P≤0.05) upregulation in the expression levels of *IL-1β*, *TNF-α*, *IL-10*, *COX-2*, *iNOS*, *TGF-β1*, *MCP-1*, and *NF-κB* genes in colon tissues of acetic acid-induced UC rats (G2) in comparison with the normal control (G1) group (Figure 2). This expression was significantly downregulated following the administration of oleuropein (G3). The expression levels in the treated group G3 remained significantly higher than that in the normal control group (G1).

Oleuropein effect on the relative expression of apoptotic genes in colon tissues

The qPCR data revealed a significant (P≤0.05) upregulation of *Bax* and downregulation of *Bcl2* genes in colon tissues of acetic acid-induced UC rats (G2) as compared to the normal control (G1) (Figure 3). This expression was significantly (P≤0.05) upregulated for *Bcl2* and downregulated for *Bax* genes following administration of oleuropein (G3) compared to G2. The expression level of *Bax* in the treated group G3 remained

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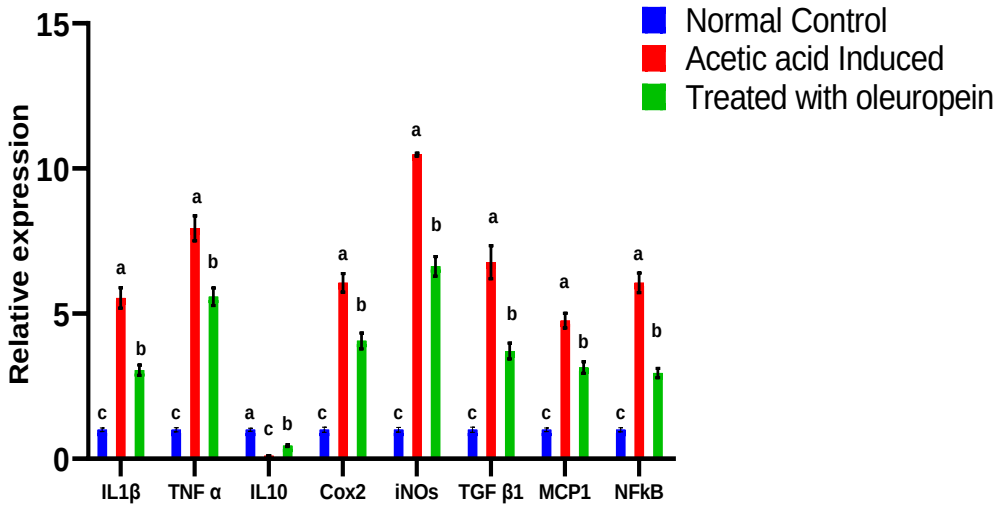


Fig. 2. The expression levels of cytokines in colon tissues and the effect of oleuropein. Values are expressed as mean ± SEM. For each parameter, mean values within columns carrying different superscript letters [a (highest) – c (lowest)] were significantly different at $P \leq 0.05$.

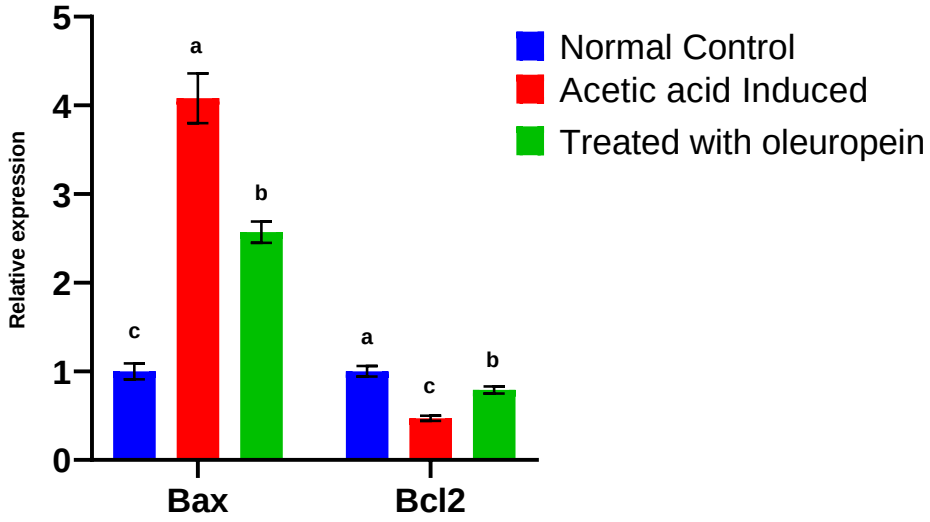


Fig. 3. The expression levels of apoptotic genes in colon tissues and the effect of oleuropein. Values were expressed as mean ± SEM. For each parameter, mean values within columns carrying different superscript letters [a (highest) – c (lowest)] were significantly different at $P \leq 0.05$.

significantly ($P \leq 0.05$) higher than that in the normal control group (G1).

Discussion

Until now, the main treatment of UC aimed to reduce the symptoms, and improve the quality of life by decreasing the morbidity rate. DAI is astandard for scoring according to the symptoms. DAI is known as a main indicator for judging the disease degree, and estimating the treatment effectiveness (19). Previous studies have demonstrated that treating the animal with acetic acid to develop colitis closely resembles that of UC in humans (20, 21). In the present study, acetic acid induced colitis (G2) caused body weight loss (as indicated by increased DAI scores), expansion of ulcerative areas, and increased colon weight in comparison with the normal control group (G1).

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We also demonstrated the oleuropein effectiveness in treating UC, and its effect on the antioxidative stress and antioxidant activity through measuring MDA, MPO, NO, SOD, CAT, and GPX levels. Also, molecular analyses for pro-inflammatory cytokines such as *IL-1β*, *TNF-α*, *IL-10*, *COX-2*, *iNOS*, *TGF-β1*, *MCP-1*, and *NF-κB* were performed. In addition, the pro-apoptotic gene *Bax* and the anti-apoptotic gene *Bcl2* expressions were assessed in rats' colon tissues. Our findings showed that there was not any mortality in the normal control group (G1) and the group treated with oleuropein (G3) during the whole experiment period. While the positive control group (G2) showed 20% mortality rate. Our results revealed the positive effect of oleuropein in reducing the mortality rate as a result of UC. Among UC symptoms, weight loss was detected in 10-15% of G3 animals. Loose stool was also detected in G3, but other symptoms (occult/gross bleeding) were not detected in this group with significant reduction in DAI score ($P \leq 0.05$), in agreement with Abu-Gharibeh et al. who reported the reduction in DAI score in mice due to the antioxidant effect of olive oil (22). Moreover, our results revealed that the colon weight was lower in the treated group than in the positive control group, while the colon length decreased in the positive control group and increased in the treated group. Our results were in line with previous studies which reported that the average colon length significantly decreased in the positive control mice (23, 24). Activated phagocytic leukocytes and neutrophils are capable of overproducing ROS in inflamed mucosa; excessive levels of which contribute to the pathogenesis of inflammatory ulcerative disease (8). Furthermore, both the activation of *iNOS*, *COX-2*, and the subsequent elevation of end products, such as NO, damage the large intestinal mucous membranes by producing free radicals, and suppressing the antioxidative system (25). Our findings showed significant elevation in colon MDA, MPO, and NO levels and a significant decline in colon SOD, CAT, and GPX in group 2 in comparison with the normal control (G1). While animals treated with oleuropein showed significant reduction in colon MDA, MPO, and NO levels and a significant elevation in SOD, CAT, and GPX levels. El-Akabawy and El-Sherif revealed that MDA, a commonly used indicator of lipid peroxidation and oxidative stress, was elevated in acetic acid induced rats, while the enzymatic activity of antioxidants such as SOD, CAT, and GSH were reduced (26). Our results are also in agreement with the findings of Ebrahimi and Hajizadeh who reported that treatment with olive leaf methanolic extract restored the activity of antioxidant enzymes SOD, GPX, GRX, and CAT and also decreased MDA (27). This suggests that oleuropein has a great antioxidant and radical scavenging activity. The intense local immune response involved in UC includes recruitment of lymphocytes and macrophages, followed by release of pro- inflammatory cytokines and inflammatory mediators (28). Many studies have shown that acetic acid colitis mimics acute human intestinal inflammation by stimulating vasopermeability, prolonging neutrophil infiltration, and inducing the production of inflammatory mediators (29-31). Our gene expression analyses revealed a significant ($P \leq 0.05$) up-regulation of *IL-1β*, T*NF-α*, *IL-10*, *COX-2*, *iNOS*, *TGF-β1*, *MCP-1*, and *NF-κB* in colon tissues of acetic acid-induced UC rats (G2) as compared to the normal control (G1), while the expression was significantly downregulated in oleuropein treated group (G3) which demonstrated that oleuropein can modulate pro-inflammatory cytokines and mediators in an animal model of colitis. In agreement with Ahmed who reported that olive leaf extract is effective in reducing IL-1β and TNF-α levels (32), Larussa et al. reported that the expression of *COX-2* significantly decreased in subjects treated with olive leaf extract (4). Also, Vajdian et al.reported *IL-10* downregulation as a result of olive leaf extract treatment (33). Serra et

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al. reported that the phenolic extract inhibited *iNOS* induction (34) and Al-rasheed et al. reported the downregulation of *NF-κB* and *TGF-β* as a result of treatment with different natural antioxidants (35). Since we found that the expression of *Cox2* and iNos significantly reduced in oleuropein treated group (G3), this suggests that the oleuropein may induce anti-inflammatory effects in colonic tissue. Our results support the concept that inhibitors of both inducible enzymes are effective anti-inflammatory agents, which represents an important mechanism to improve the UC development. Also, our study revealed a significant ($P \leq 0.05$) upregulation of *Bax* and downregulation of *Bcl2* in acetic acid treated group (G2) in comparison with the normal control group (G1), thereby decreasing the *Bcl2/Bax* ratio. However, oleuropein treatment elevated the *Bcl2/Bax* ratio in G3 in comparison with G2, suggesting an antiapoptotic property for oleuropein. Similarly, Almeer and Abdel Moneim reported that olive leaf extract treatment inhibited apoptosis by up-regulating *Bcl-2* and downregulating *Bax* (36). Al-Quraishy et al. also stated that the antiapoptotic activity of olive leaf extract is due to its antioxidant and anti-inflammatory properties (37).

Our study concludes the beneficial effects of oleuropein, as it reduces the mortality rate and DAI in comparison with the positive control group. We demonstrated the ability of oleuropein to counteract oxidative stress and inflammation. Oleuropein caused a significant reduction in colon MDA, MPO, and NO levels and a significant elevation in SOD, CAT, and GPX levels and caused down regulation of proinflammatory cytokines (*IL-1β*, T*NF-α*, *IL-10*, *COX-2*, *iNOS*, *TGF-β1*, *MCP-1*, and *NF-κB*). Also, the pro-apoptotic gene *Bax* was downregulated and the anti-apoptotic gene *Bcl2* was upregulated as a result of oleuropein treatment in comparison with untreated group (G2). Further clinical and experimental trials are required to clarify the exact molecular mechanisms of oleuropein action in UC treatment.

Conflict of interest

Authors declare no conflict of interest.

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