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Olive (*Olea europaea*) leaf methanolic extract prevents HCl/ethanol-induced gastritis in rats by attenuating inflammation and augmenting antioxidant enzyme activities

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ABSTRACT

Gastritis is preponderantly characterized by inflammation of the lining epithelial layer and the chronic gastritis is considered as a pre-cancer lesion. For many centuries olive (*Olea europaea*) leaf has been used for its putative health potential, nonetheless, to date, the gastroprotective effects of olive leaves have not been studied yet. Hence, in this study we investigated whether olive leaf extract (OLE) could protect gastric mucosa against HCl/ethanol-induced gastric mucosal damage in rats. Hcl/ethanol administration caused significant damage to the gastric mucosa, as confirmed by gastric ulcer index and histological evaluation. However, this damage was largely prevented by pre-administering 20 mg/kg omeprazole or 100 mg/kg OLE. Interestingly, the damage was completely prevented by pre-administering 200 and 300 mg/kg OLE. Moreover, OLE attenuated the inflammatory response by decreasing nuclear factor-κB (NF-κB), cycloxygenase-2 (COX-2) and tumor necrosis factor-α (TNF-α) expressions, and down-regulating inducible nitric oxide synthase (iNOS) and interleukin-1β (IL-1β) in gastric mucosa. The gastroprotective mechanism of OLE involved the promotion of enzymatic and nonenzymatic molecules (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione reduced form), promoting nuclear factor erythroid 2-related factor 2 (Nrf2) mRNA expression, halting lipid peroxidation and preventing the overproduction of nitric oxide. Together, our findings clearly demonstrated that OLE could prevent HCl/ethanol-induced gastritis by attenuating inflammation and oxidant/antioxidant imbalance. Indeed, OLE could potentially be useful as a natural therapy for gastritis.
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1. Introduction

The gastrointestinal tract carries out the fundamental function of turning food into nutrients and delivering it to each cell within the body. The stomach could be a main organ occupied the higher part of the gastrointestinal tract, and it vigorously churns the food to crash it mechanically as well as with chemicals. It is well documented that gastric malady might lead to dyspepsia (indigestion), and may cause malnutrition and weight loss [1]. Gastritis is preponderantly characterized by inflammation of the lining epithelial layer of gastric mucosa in the stomach and is the most common higher gastrointestinal acid-related malady of the digestive tract, markedly poignant several individuals worldwide [2]. Gastritis is leading to abdominal pain, heart burn, possible bleeding, and different gastrointestinal symptoms. Furthermore, chronic gastritis is a pre-cancer lesion [3]. The complex etiology of gastritis comprises microorganism infection, extravagant alcohol consumption, emotional distress, free radicals, certain medicines such as steroidal and non-steroidal anti-inflammatory drugs (SAIDs and NSAIDs), and nutritional insufficiencies that disrupting the gastric mucosal barrier and making it at risk of the ordinary stomachal secretions [4].

Abbreviations: CAT, catalase; COX-2, cycloxygenase-2; GPx, glutathione peroxidase; GRd, glutathione reductase; GSH, glutathione; GUI, gastric ulcer index; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LPO, lipid peroxidation; MDA, malondialdehyde; NF-κB, nuclear factor-κB; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; OLE, olive leaf extract; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α.

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Reactive oxygen species (ROS) has been well reported as a stress operator in the gastric mucosa as well as the lining epithelial layer of stomach in the immediate vicinity [5]. The minimizing risk of stomach cancer or gastritis with the dietary supplementation of antioxidants like plant polyphenols, carotenoids, α-tocopherol and ascorbic acid support the fundamental role of ROS in the gastric ulcers and cancer formation [6]. Over and above, the levels of these antioxidants are diminished during the *Helicobacter pylori* infection, which leads to ROS accumulation in the epithelial layer of stomach [7].

Olive tree (*Olea europaea*, Oleaceae) is a longevous tree with economical, social, and cultural values to the inhabitants of Mediterranean basin. The leaves of this plant have been used for many centuries in the traditional medicine to cure diabetes and to prevent or cure malaria symptoms [8]. The medicinal characteristics of olive leaves have focused on its polyphenols namely, oleuropein (is the principal member of the family of secoiridoids in the olive tree) and hydroxytyrosol (is one of the main phenolic components of olive oil), which according to different studies done in vivo and in vitro, those polyphenols have antioxidant, hypoglycaemic, antitumor, hypotensive, antimicrobial, hypocholesterolmiant and antiinflammatory efficacies [9]. Additionally, the leaves of olive contain a significant quantity of flavonoids such as luteolin-7-*O*-glucoside, luteolin-7-*O*-rutinoside, apigenin-7-*O*-glucoside, rutin, luteolin, and apigenin [10]. Sudjana et al. [11] have demonstrated that olive leaf extract possess gastrointestinal protective properties may have a role in modulating the composition of the gastric microflora by selectively reducing the amounts of *Campylobacter jejuni* and *Helicobacter pylori*. These findings suggested that olive leaf extract (OLE) may be useful as a lead ingredient or new agent for preventing and treating gastrointestinal maladies. Hence, in the current study, olive leaf extract was studied for their gastroprotective activity against acidified ethanol-induced gastric ulcer in a rat model.

2. Materials and methods

2.1. Preparation of OLE

Olive leaves were purchased from local market in Cairo, Egypt. The identity of this leaf was confirmed by taxonomist (A voucher specimen has been stored in Herbarium of Botany department at Helwan University, Egypt [HCH No. s.n. 2017]). Olive leaves were washed under running tap water to remove dust, air dried at room temperature that not exceeding 35 °C, then the leaves were ground into a powder using an electrical pulverizer. The prepared powder was extracted with 70% (v/v) methanol in the dark for 48 h at 4 °C with mixed from time to time. OLE was clarified using Whatman grade 1 filter paper to remove any plant residues. Subsequently, the supernatant was then evaporated to semi-dryness in a vacuum evaporator (IKA, Germany). The semi-dried residue was then frozen at −80 °C prior to lyophilisation to solidify any liquid (eg. moisture) in the samples. The residue was dissolved in distilled water and stored at −20 °C in dark bottle until used in this experiment. The concentration of polyphenolics and flavonoids compounds was determined in the OLE using standard methods. The total phenolics content of OLE ranged from 106.2 to 118.3 mg/g extract whereas, the total flavonoids content ranged from 55.2 to 62.4 mg/g extract.

2.2. HPLC analysis

The analysis of oleuropein with other bioactive polyphenolic and flavonoid constituents present in the OLE was performed using a Perkin Elmer Series 200 liquid chromatography (PerkinElmer, USA) according to the method of Grizis et al. [12].

2.3. Experimental animals

Ten week old male Wistar albino rats (specific pathogen-free), weighing 180–200 g were used for the acute toxicity study and HCl/Ethanol-induced gastritis experiment. All the animals used in these experimentations were purchased from the animal facility of the Holding Company for Biological Products and Vaccines (Cairo, Egypt). The animal housing condition was as described previously [13]. All of the experimental procedures were approved by the Institutional Animal Ethics Committee guidelines for animal care and use at Helwan University, and were conducted according to the European Community Directive (86/609/EEC) the national rules on animal care that was carried out in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals 8th edition.

2.4. Acute toxicity study

Acute toxicity study was carried on male Wistar albino rats. Rats were divided into two groups vehicle control and OLE of 5 rats each. Rats were allowed to acclimatize for a week before study. The rats were fasted for 24 h before dosing with OLE with access to adequate drinking water. The treated rats administered OLE orally at a dose of 1000 mg/kg bwt, and the control rats administered saline by gavage. Rats of the two groups were observed individually for any signs of toxicity within the first 6 h after the treatment. The mortality was assessed and recorded if any for 14 days after the treatment.

2.5. HCl/Ethanol-induced gastritis in rats

Forty-nine rats were randomly assigned to seven groups, 7 rats in each, and fasted for 24 h prior to oral dosing with the normal saline solution (positive group), omeprazole (a standard treatment control at a dose of 20 mg/kg bwt [14] obtained from Borg Pharmaceutical Ind., Egypt), or OLE at a dose of 100, 200 and 300 mg/kg bwt. One hour later, all the rats orally administered 5 ml/kg bwt of a mixture of 0.15 M HCl (Sigma, St. Louis, MO, USA) and 60% ethanol (Sigma, St. Louis, MO, USA) solution according to Son et al. [15]. The normal control group and OLE control group received only vehicle (normal saline solution) and OLE at a dose of 300 mg/kg bwt, respectively. Rats were killed by cervical dislocation 2 h after the administration of HCl/ethanol solution, the stomach was quickly removed and fixed in 4% neutral formalin solution for 1 h, opened by an incision along the greater curvature, and photographed using Samsung camera (WB30F, Japan). Total area (mm^2) of mucosal erosive lesion was determined using ImageJ 1.50i (National Institutes of Health (NIH), USA) software. The percentage of ulcer inhibition by OLE was calculated by the following equation:

$$\% \text{ ulcer inhibition} = [(\%U_{area} \text{ untreated ulcer control} - \%U_{area} \text{ OLE treated ulcer rat})/\%U_{area} \text{ untreated ulcer control}] \times 100$$

where $\%U_{area}$ is the percent ulcerated or hemorrhagic area of the total gastric mucosa area.

2.6. Gastric ulcer index (GUI) determination

Gastric mucosal injury degree was estimated for gross pathology based on a 0–5 scoring method derived from the number and severity of gastric lesions as previously described by Arab et al. [16]: 0 = no lesions; 1 = tiny hemorrhagic lesions; 2 = lesions < 2 mm; 3 = lesions 2–3 mm; 4 = lesions 3–4 mm; 5 = lesion > 4 mm. The score was multiplied by 2 when the width of the erosion is greater than 1 mm. The mean score was calculated and expressed as the GUI. The GUI was identified by a blind observer.

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