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# Antiulcerogenic activity of *Zizyphus lotus* (L.) extracts

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**Abstract**

Oral administration of aqueous extracts of *Zizyphus lotus* root barks (50–200 mg/kg) leaves (50–200 mg/kg) and fruits (200–400 mg/kg) produced a significant ($p < 0.01$) and dose dependent inhibition to the acute ulcer induced by HCl/ethanol solution. The methanolic (MeOH), ethyl acetate (EtOAc) and chloroformic ($CHCl_3$) leaves extracts when administered orally at the dose of 200 mg/kg, exhibited a significant ($p < 0.01$) inhibition of gastric lesions by 45%, 76% and 33%, respectively. Indeed, methanolic and ethyl acetate root barks extracts significantly reduced the gastric lesions by 47% and 41%, respectively. While the chloroformic root barks extract had no significant activity (19%). The effect of all extracts was compared with cimetidine (100 mg/kg, 62%) and omeprazole (30 mg/kg, 93%). Volume, pH and acidity of gastric juice were studied in pylorus-ligated rats. Root barks (200 mg/kg, $p < 0.01$), leaves (200 mg/kg, $p < 0.01$) and fruits (400 mg/kg, $p < 0.05$) aqueous extracts showed significant reduction of gastric juice secretion in pylorus ligated rats, whereas the other extracts did not show any significance. Thus, *Zizyphus lotus* extracts act essentially as cytoprotective agents, which support the antiulcer effect of this plant in the traditional medicine.


*Keywords:* Rhamnaceae; *Zizyphus lotus*; Antiulcerogenic activity; Gastric ulcer; Mucus secretion

## 1. Introduction

In gastrointestinal disorder, ulcer requires a well targeted therapeutic strategy. A number of drugs including proton pump inhibitors and $H_2$ receptor antagonists are available for the treatment, but clinical evaluation of these drugs showed an incidence of relapses, side effects, and drug interactions (McIntosh et al., 1991; Piper, 1995; Sontag, 1997). This medication has been the cause for the development of new antiulcer drugs and the search for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Although, it is generally accepted that ulcer results from an imbalance between aggressive factors and the defence mechanism (Charlet et al., 1985). To regain the balance, drugs of plant origin are investigated to inhibit the gastric acid secretion or to activate the mucosal defence mechanism by increasing mucus production (Borrelli and Izzo, 2000). Medicinal plants provide an important source of new chemical substances with potential therapeutic effects. They have been used in traditional medicine for the treatment of several diseases. The present study investigates the antiulcerogenic activity of *Zizyphus lotus* (Rhamnaceae). This plant is known for its several medicinal values as anti-inflammatory and analgesic drug (Borgi et al., 2007), thus, it was used topically as emollient in the treatment of boils and it is described as having antiulcer activity (Le-Floc'h, 1983). Aqueous and organic extracts of *Z. lotus* are characterized by the presence of flavonoids and tannins. The objective of this study was to evaluate the antiulcer activity of a serial extracts obtained from the root barks, leaves and fruits of *Z. lotus*.

## 2. Materials and methods

### 2.1. Plant materiel

Plant of *Z. lotus* including the root barks, leaves and fruits was collected from the locality of Cherahil (Monastir, Tunisia). The plant was identified in the laboratory of Botanic, Faculty of Pharmacy-Monastir. A voucher specimen (No. 0269) was deposited in the herbarium of the Laboratory of Pharmacognosy (Faculty of Pharmacy Monastir, Tunisia).

### 2.2. Extraction

Root barks (RB), leaves (L) and fruits (F) of *Z. lotus* were air dried, powdered and extracted separately as aqueous decoction

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Table 1
Phytochemical screening of *Z. lotus* extracts

| Extracts | Yield (%, w/w) | Flavonoids | Tannins | Saponins | Alkaloids |
|---|---|---|---|---|---|
| Aq ext RB | 14.38 | ++ | ++ | ++ | + |
| MeOH ext RB | 25.27 | ++ | ++ | ++ | + |
| EtOAc ext RB | 1.29 | + | ++ | + | − |
| $CHCl_3$ ext RB | 0.03 | + | − | + | − |
| Aq ext L | 17.68 | ++ | ++ | ++ | − |
| MeOH ext L | 15.28 | ++ | ++ | + | − |
| EtOAc ext L | 2.37 | − | ++ | − | − |
| $CHCl_3$ ext L | 4.28 | − | − | + | − |
| Aq ext F | 34.05 | + | + | + | + |

(+): Detectable; (−): not detectable. (Aq ext: aqueous extract, MeOH ext: methanolic extract, EtOAc ext: ethyl acetate extract, $CHCl_3$: chloroformic extract, RB: root barks, L: leaves, F: fruits).

(Aq ext) by boiling during 15 min. Other specimen of root barks and leaves were taken separately and extracted exhaustively in a Soxhlet apparatus with chloroform ($CHCl_3$ ext), ethyl acetate (EtOAc ext) and methanol (MeOH ext). On complete evaporation of these solvents, the extracts were freeze-dried. The yield of different extracts was shown in Table 1.

### 2.3. Phytochemical tests

The dry extracts of root barks, leaves and fruits of *Z. lotus* were separately tested for the presence of flavonoids, tannins, saponins and alkaloids (Dahou et al., 2003).

### 2.4. Animals

Wistar rats of either sex, weighing 150–200 g, provided from Pasteur Institute (Tunis, Tunisia) were used in this study. Animals were maintained under standard environmental conditions and had free access to standard rodent feed and water. Housing conditions and in vivo experiments were approved according to the guidelines established by the European Union on Animal Care (CCE Council 86/609).

### 2.5. Drugs and chemicals

The drugs used in this study are: cimetidine from Medis (Tunis, Tunisia), omeprazole from AstraZeneca (Monts). The chemicals used were all of analytical reagent grade. All drugs and reagents were prepared immediately before use.

### 2.6. Gastric lesions induced by HCl/ethanol

The anti-ulcerogenic activity of aqueous, MeOH, EtOAc and $CHCl_3$ extracts derived from *Z. lotus* was studied in 150 mM HCl/EtOH induced gastric ulcer (Hara and Okabe, 1985). Rats were allotted into different groups, fasted for 24 h prior receiving an oral dose of saline (NaCl 9‰, 5 ml/kg), aqueous extract (50, 100 and 200 mg/kg), methanolic, ethyl acetate or chloroformic extracts at the same dose 200 mg/kg. Two other groups, received cimetidine (100 mg/kg, p.o) and omeprazole (30 mg/kg, p.o) as reference compounds. After 30 min, all groups were orally treated with 1 ml of 150 mM HCl/EtOH (40:60, v/v) solution for gastric ulcer induction. Animals were killed 1 h after the administration of ulcerogenic agent; their stomachs were excised and opened along the great curvature, washed and stretched on cork plates. The surface was examined for the presence of lesions and the extent of the lesions was measured. The summative length of the lesions along the stomach was recorded (mm) as lesion index.

### 2.7. Gastric secretion parameters

Gastric secretion volume, pH and HCl concentration were measured according to the method of Shay et al. (1945). All groups of rats were fasted 24h, with free access to water. Immediately after pylorus ligature, NaCl 9‰ (5 mg/kg), different *Z. lotus* extracts, cimetidine (100 mg/kg) and omeprazole (30 mg/kg) were administered intraduodenally. After 4 h, animals were killed by cervical dislocation, the abdomens were opened, the stomachs were removed and the gastric content was collected to determine the total amount of gastric juice (ml) and pH values. Total acid in the gastric secretion was determined by titration to pH 7.0 with 0.1 N NaOH.

### 2.8. Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Dunnett's *t*-test for multiple comparisons. The significance of difference was accepted at $p < 0.05$.

Table 2
Effect of *Z. lotus* root barks, leaves and fruit extracts on gastric ulcer induced by HCl/ethanol in rats

| Treatment | Dose (mg/kg) | Ulcer index (mm) | Inhibition (%) |
|---|---|---|---|
| Control 1 | – | 56.10 ± 3.55 | – |
| Aq ext RB | 50 | 22.61 ± 3.30** | 60 |
| Aq ext RB | 100 | 20.44 ± 3.49** | 64 |
| Aq ext RB | 200 | 2.94 ± 2.03** | 95 |
| MeOH ext RB | 200 | 29.50 ± 6.31** | 47 |
| EtOAc ext RB | 200 | 33.26 ± 4.39** | 41 |
| $CHCl_3$ ext RB | 200 | 45.45 ± 2.48$^{ns}$ | 19 |
| Aq ext L | 50 | 28.33 ± 1.66** | 50 |
| Aq ext L | 100 | 27.71 ± 3.34** | 51 |
| Aq ext L | 200 | 25.87 ± 5.69** | 54 |
| MeOH ext L | 200 | 30.99 ± 2.46** | 45 |
| EtOAc ext L | 200 | 13.55 ± 1.78** | 76 |
| $CHCl_3$ ext L | 200 | 34.72 ± 7.36** | 33 |
| Control 2 | – | 64.21 ± 1.49 | – |
| Aq ext F | 200 | 47.90 ± 4.34* | 25 |
| Aq ext F | 300 | 41.66 ± 5.30** | 35 |
| Aq ext F | 400 | 29.98 ± 0.53** | 53 |
| Control 3 | – | 55.80 ± 2.87 | – |
| Cimetidine | 100 | 21.33 ± 1.02** | 62 |
| Omeprazole | 30 | 4.00 ± 0.54** | 93 |

Data are expressed as mean ± S.E.M. ($n = 6$), *$p < 0.05$; **$p < 0.01$; ns: not significant vs. control. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett't test for multiple comparison. (Aq ext: aqueous extract, MeOH ext: methanolic extract, EtOAc ext: ethyl acetate extract, $CHCl_3$: chloroformic extract, RB: root barks, L: leaves, F: fruits).