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Prophylactic and curative anti-ulcerogenic activity and the possible mechanisms of action of some desert plants

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KEYWORDS

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MDA;
Reduced GSH

Abstract The present study aimed to evaluate the anti-ulcerogenic activities and the possible mechanisms of action of seven desert plants from different families. *Conyza dioscoridis* (L.) Desf. (Asteraceae), *Euphorbia hirta* L. (Euphorpiaceae), *Origanum syriacum* L., *Salvia* lanigera L. (Lamiaceae), *Sisymbrium irio* L., *Solanum nigrum* Linn. (Solanaceae) and *Solenostemma arghel* (Del.) Hayne. (Asclepiadaceae), were tested using prophylactic and curative models of absolute ethanol-induced ulcer, at three doses (125, 250 & 500 mg/kg) of each extract.

The investigated extracts possessed dose dependent anti-ulcerogenic activities in both models, with LD_{50} higher than 5 g/kg. The most effective extracts were *C. dioscoridis* and *S. irio* with percent protection of control ulcer; 91.1% and 85.4% respectively. The antisecretory activity of both *C. dioscoridis* and *S. irio* appears to be mainly related to the suppression of gastrin release. The *in vitro* potential radical (DPPH) scavenging activities of the investigated extracts were well supported with the reduction in gastric MDA (50.6% and 43.3%) and enhancing the level of reduced GSH (2.84, 2.59 mg/g tissue) for *C. dioscoridis* and *S. irio* respectively. In addition, suppression of the inflammatory mediator TNF-α may be one of the possible mechanisms of action. The alcohol extracts of *C. dioscoridis* and *S. irio* showed no alteration on liver and kidney functions.

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Phytochemical screening of the investigated extracts revealed the presence of flavonoids, tannins and sterols which could be related to the activities.

1. Introduction

Peptic ulcer is a disease among the most dominant chronic diseases that affect the world's population. It develops when there is an imbalance between the aggressive and protective factors at the luminal surface of the epithelial cells (Kalant et al., 2007). The principal factors causing this disease are inadequate dietetic habits, prolonged use of non-steroidal anti-inflammatory drugs, stress and infection by *Helicobacter pylori*, in addition to other factors of genetic origin. Characteristic features include epigastric pain, nocturnal pain and vomiting (Waller et al., 2005).

Several classes of pharmacological agents have been proved effective in the management of the acid peptic disorders, these groups include Antacids, antisecretory drugs (Proton pump inhibitors, antihistaminic (H_2) and anticholinergic (M_1)) and cytoprotective (sucralfate and prostaglandin analogues) agents (Julian and David, 1962; Katzung, 2004) in addition to antimicrobial for eradication of *H. pylori* (Kalant et al., 2007).

In the search of new anti-ulcerogenic agents, special interest has been directed to the herbal based products. Many plant extracts and natural isolated compounds were reported to have potential anti-ulcerogenic activity (Awaad et al., 2013).

The investigated extracts were reported to possess variable pharmacological properties. Anti-inflammatory and analgesic activities were reported for *C. dioscoridis*, *O. syriacum* (Awaad et al., 2011), *E. hirta* (Martinez et al., 1999; Lanhers et al., 1991) and *S. nigrum* (Zainul et al., 2006). Both *C. dioscoridis* and *E. hirta* extracts showed anti-diarrheal (Atta and Mounier, 2004; Galvez et al., 1993), antidiabetic (Shabana et al., 1990; Kumar and Rashmi, 2010) and antimicrobial activities (El-Hamouly and Ibrahim, 2003; Rajeh et al., 2010). Four extracts were potential antioxidants: *C. dioscoridis S. nigrum*, *S. lanigera* and *O. syriacum* (Awaad et al., 2011; Karmakar et al., 2010; Tenore et al., 2011; Alma et al., 2003).

Solanum nigrum extract is a potent antiulcerogenic agent with H^+/K^+ATPase inhibitory activity (Jainu and Shyamala, 2006) in addition to its hepatoprotective potential (Raju et al., 2003).

2. Material and methods

2.1. Plant materials

The aerial parts of seven desert plants from different families (*Conyza dioscoridis* (L.) Desf. (Asteraceae), *Euphorbia hirta* L. (Euphorpiaceae), *Origanum syriacum* L. and *Salvia lanigera* L. (Lamiaceae), *Sisymbrium irio* L., *Solanum nigrum* Linn. (Solanaceae) and *Solenostemma arghel* (Del.) Hayne. (Asclepiadaceae)) were collected from certain localities in Egyptian deserts in spring during flowering stage of 2012.

The samples were kindly identified by Dr. Ahmed Morsy, Professor of Botany, Desert Research Centre and compared with the published plants description (Täckholm, 1974; Boulos, 2000). Voucher specimens have been deposited in the herbarium of Desert Research Centre. Plant materials were air-dried separately in shade, reduced to fine powder, packed in tightly closed containers and stored for phytochemical and pharmacological studies.

2.2. Animals

Swiss albino mice of both sex (26–30 g) and male Wistar rats (180–200 g) were used. Animals were maintained under standard conditions (temperature 23 ± 1.0 °C, humidity 55 ± 10%, 12 h light/12 h dark cycle) and housed in standard polypropylene cages with wire mesh top and they fed with a standard pellet diet with water *ad libitum* and were allowed to adapt to the laboratory environment for one week before experimentation.

2.3. Extraction

For each plant, three hundred grams were separately extracted using ethanol (95%) in a Soxhlet apparatus till complete exhaustion. The total alcohol extracts were concentrated under reduced pressure at a temperature not exceeding 35 °C to yield a dry extract. The residue obtained for each extract was weighed.

Known weight of each extract was freshly prepared by dissolving in distilled water or suspending by the aid of few drops of Tween 80 just before the administration.

2.3.1. Phytochemical screening

Powdered samples from the aerial parts of the investigated plants were subjected to preliminary phytochemical screening according to the published methods (Trease and Evans, 2002; Sofowora, 1993; Harborne, 1973).

2.4. Acute toxicity (LD_{50}) test

Swiss albino mice in groups of six, received one of 100, 500, 1000, 2000, or 5000 mg/kg doses of the extracts to be tested. Control animals received the vehicle and were kept under the same conditions. Signs of acute toxicity and number of deaths per dose within 24 h were recorded for determination of oral median lethal dose, LD_{50} (Lorke, 1983).

2.5. Anti-ulcerogenic activity

Two sets of male Wistar rats were used in this study: the first set was for the prophylactic model, while the other set was designed for the curative model. In each set, 24 groups each of 6 animals were used. Rats of groups 1 and 2 received the vehicle (5 mL/kg) and served as normal control and ulcer control groups. Group 3 administered lansoprazole (30 mg/kg) and served as Reference Drug group. Rats of groups 4–24

received the total alcohol extracts of the seven investigated extracts at doses 125, 250 and 500 mg/kg.

All medications were administered orally once daily for 3 consecutive days. In the prophylactic model the last dose was administered 30 min before ulcer induction, while in the curative model, the first dose was administrated 1 h after ulcer induction.

Induction of peptic ulcer was carried out using absolute ethanol-induced ulcer method described by Suleyman et al. (2002) for the prophylactic model while the curative model was first described. Assessment of gastric lesions was carried out according to Cho and Ogle (1979).

Lesion scores were quantified by the scoring system (0–5) (Morris et al., 1989). Ulcer indices (mm) were calculated as the sum of the total length of long ulcers and petechial lesions in each group of rats divided by its number. The percent of protection was determined according to the formula:

$$\% \text{ Protection of control ulcer} = (\text{Control UI} - \text{Test UI}/\text{Control UI}) \times 100$$

2.6. Antioxidant activity (in vitro)

The antioxidant activity was evaluated using DPPH free radical scavenging activity method described by Sreejayan and Rao (1996). Radical scavenging activity was obtained from the following equation:

$$\text{Radical scavenging activity } \% = \{(\text{Ac} - \text{At})/\text{Ac}\} \times 100.$$

where Ac was the absorbance of control (DPPH) and At was the absorbance of test compound (certain concentration of extract), at each time.

2.7. Possible mechanisms of action (biochemical investigations) for the most effective extracts

The total alcohol extracts of *C. dioscoridis and S. irio* (250 and 500 mg/kg) were administrated to four groups of animals ($n = 6$). Three other groups of animals were used, two received water orally and the third received oral lansoprazole (30 mg/kg) to serve as normal control, ulcer control and standard groups respectively. All medications were administrated for 3 successive days. One hour after the last dose, peptic ulcer was induced by oral administration of absolute ethanol (1 ml/200 g/kg). All rats were sacrificed by an overdose of chloroform, the stomachs were rapidly removed, blood samples were collected and different biomarkers were measured.

2.7.1. Determination of gastric thiobarbituric acid reactive substances (TBARS) or (Malondialdehyde; MDA) content, using a kit supplied by Sigma-Aldrich Chemicals, USA.
2.7.2. Determination of gastric sulfhydryl compound (reduced glutathione GSH) content, using a kit supplied by Sigma-Aldrich Chemicals, USA.
2.7.3. Determination of serum gastrin level, using ELISA kit supplied by Ray Biotech, Inc., USA.
2.7.4. Determination of plasma TNF-α (Tumor Necrosis Factor- alpha), using ELISA kit supplied by Ray Biotech, Inc., USA.
2.7.5. Determination of basic fibroblast growth factor (BFGF), using ELISA kit supplied by Glory Science Co., Ltd, USA.

2.8. Sub-chronic toxicity

Thirty rats were randomly divided into three groups. Rats of the 1st group received the vehicle in a dose of 5 mL/kg and left as normal control. Rats of the 2nd and 3rd groups were administered the alcohol extracts of *C. dioscoridis and S. irio* (500 mg/kg). All medications were administered orally daily for 35 consecutive days. Animals were maintained under identical conditions with food and water *ad libitum* for the entire period with close observation. At the end of the experimental period, blood samples were collected, and sera were separated to be used for the biochemical estimations.

2.8.1. Measurement of liver and kidney function markers

Liver functions were evaluated by measuring the serum activity of ALT and AST (Reitman and Frankel, 1957). Serum concentrations of urea (Wills and Savory, 1981) and creatinine (Kroll et al., 1987) were determined colorimetrically as measures of kidney functions.

2.9. Statistical analysis

All values were expressed as mean ± S.D. Comparisons between means were carried out using one-way ANOVA test followed by Tukey's HSD test using SPSS, version 14.

Statistical significance of differences between two means was assessed by unpaired Student's *t*-test. Differences at $p < 0.05$ were considered statistically significant.

3. Results and discussion

Phytochemical screening of the investigated extracts revealed the presence of carbohydrates, flavonoids, tannins, unsaturated sterols, proteins and lactones which could be the active materials responsible for the activities.

3.1. Acute toxicity (LD_{50}) test

Neither morbidity nor mortality were recorded in mice treated with any of the tested extracts during 24 h of observation. Doses from 0.1 up to 5 g/kg did not produce any symptom of acute toxicity (diarrhea, hematuria, restlessness, uncoordinated muscle movements, and respiratory distress). It was suggested that oral LD_{50} of the evaluated extracts were higher than 5000 mg/kg. Since substances possessing LD_{50} higher than 50 mg/kg are non-toxic (Buck et al., 1976), the tested extracts were considered safe.

3.2. Anti-ulcerogenic activity

Ethanol-induced gastric ulcers model has been widely used for the evaluation of gastro protective activity. Ulcers caused by ethanol are due to superficial damage to mucosal cells (Miller and Henagan, 1984). Mucosal blood flow is an important factor in the damage caused by alcohol and could be mod-

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ulated by prostaglandins (Hollander et al., 1984). The ethanol-induced ulcers are predominant in the glandular part of stomach. It was reported that, ethanol stimulates the formation of mast cell secretary products (Oates and Hakkinen, 1988), and reactive oxygen species resulting in the damage of rat gastric mucosa (Peskar et al., 1986).

Gastric damage induced by absolute ethanol in the current study was characterized by both long ulcers and petechial lesions. The number of ulcers (13.00 ± 1.67) and the ulcer index (19.23 ± 1.47) in the control rats that received ethanol were significantly increased when compared with normal untreated animals in both models (prophylactic and curative). These results were in agreement with the results of Jainu and Shyamala (2006). In the present work, lansoprazole was selected as a reference drug for ethanol model because it provides a much better protective effect on ethanol-induced gastric damage than other antiulcer drug (Cho and Ogle, 1979). Lansoprazole has an important role in gastric mucosal defense and participates in ulcer protection in ethanol-induced rats (Tsuji et al., 2002).

In the present study, all the investigated extracts were found to be effective antiulcerogenic agents at different doses (125, 250 & 500 mg/kg). Oral administration of all the investigated extracts reduced the severity of gastric damage in a dose dependent manner (Tables 1 and 2). At the high dose (500 mg/kg) four extracts (*C. dioscoridis*, *S. irio*, *S. lanigera* and *S. nigrum*) were as effective as lansoprazole (30 mg/kg) in reducing all parameters of peptic ulcer in both models (prophylactic and curative) while the activity of *O. syriacum* was similar to that of lansoprazole in the prophylactic model only.

At the dose 250 mg/kg, only *C. dioscoridis* was as effective as lansoprazole (30 mg/kg), while, the activity of all investigated extracts at the low dose (125 mg/kg) was significantly less effective than lansoprazole in both prophylactic and curative models.

The most effective extracts were *C. dioscoridis*, followed by *S. irio,* while the lowest activity was reported for *E. hirta* (Figs. 1 and 2).

3.3. In vitro antioxidant activity: DPPH free radical scavenging activity

The investigated extracts possessed different scavenging ability toward DPPH radical at concentrations of 2, 4, 6, 8 and 10 mg/ml. Among the investigated extracts, *C. dioscoridis* showed the highest scavenging activity ranged from 91.4 to 42.7%, followed by *S. arghel* (85.3–22.0%), while the lowest scavenging activity was reported for *S. nigrum* (19.8–10.7%), corresponding to 87.8% for standard ascorbic acid at concentration 100 μM. *O. syriacum* (65.6–20.2%), *S. lanigera* (62.3–30.5%) and *S. irio* (55.7–27.9%) showed considerable high scavenging activity, while *E. hirta* Linn. showed good activity ranged from 22.1 to 15.2% (Table 3).

It has been found that oxygen-derived free radicals are implicated in the mechanism of acute and chronic ulceration

Table 1 Prophylactic effect of the investigated extracts on absolute ethanol-induced ulcer in rats.

Groups	Dose (mg/kg)	Lesion score (0–5)	Number of ulcers	Ulcer area (mm^2)	Ulcer index (mm)
Ulcer control	–	4.33 ± 0.82	13.00 ± 1.67	23.51 ± 1.38	19.23 ± 1.47
Lansoprazole	30	1.22* ± 0.02	2.07* ± 0.01	4.12* ± 0.15	2.74* ± 0.03
Conyza dioscoridis	125	2.30*@ ± 0.01	3.17* ± 0.15	7.71*@ ± 1.51	4.52*@ ± 1.05
	250	2.07* ± 0.63	1.83* ± 0.75	5.22* ± 0.98	3.30* ± 1.03
	500	1.23* ± 0.41	0.67* ± 1.87	2.53* ± 0.90	1.70* ± 1.21
Euphorbia hirta	125	2.81*@ ± 0.41	6.22*@ ± 1.79	12.81*@ ± 1.17	8.00*@ ± 1.26
	250	2.71*@ ± 0.82	5.17*@ ± 0.75	11.00*@ ± 1.55	6.82*@ ± 1.17
	500	2.21*@ ± 0.75	4.83*@ ± 1.72	9.50*@ ± 1.38	5.71*@ ± 1.03
Origanum syriacum	125	3.04*@ ± 0.63	8.83*@ ± 1.60	14.01*@ ± 1.40	10.01*@ ± 1.41
	250	2.71*@ ± 0.82	4.83*@ ± 1.17	10.00*@ ± 1.10	6.21*@ ± 1.47
	500	2.20*@ ± 0.75	3.51*@ ± 1.22	7.32*@ ± 2.16	4.50* ± 1.52
Salvia lanigera	125	2.52*@ ± 0.08	7.33*@ ± 1.21	16.30*@ ± 1.20	8.70*@ ± 1.10
	250	2.03* ± 0.89	4.83*@ ± 1.17	9.20*@ ± 1.72	5.22*@ ± 1.47
	500	1.51* ± 0.05	2.54* ± 1.00	6.72*@ ± 1.03	3.21* ± 1.50
Sisymbrium irio	125	2.20*@ ± 0.05	4.17*@ ± 1.47	12.81*@ ± 1.94	9.80*@ ± 1.17
	250	1.81* ± 0.06	2.83* ± 0.08	7.20*@ ± 1.21	4.71*@ ± 1.03
	500	1.54* ± 0.05	1.50* ± 0.02	4.00* ± 0.60	2.80* ± 1.20
Solanum nigrum	125	2.20*@ ± 0.05	4.33*@ ± 1.02	15.00*@ ± 1.30	8.30*@ ± 1.60
	250	2.10*@ ± 0.08	4.01*@ ± 1.00	10.80*@ ± 1.02	5.00*@ ± 1.00
	500	1.80* ± 0.06	2.51* ± 0.05	4.50* ± 0.09	2.80* ± 0.09
Solenostemma arghel	125	2.71*@ ± 0.07	8.00*@ ± 0.89	18.20*@ ± 1.80	9.70*@ ± 1.63
	250	2.30*@ ± 0.09	4.33*@ ± 0.09	10.20*@ ± 1.94	5.71*@ ± 1.03
	500	2.17* ± 0.04	3.00* ± 0.05	9.50*@ ± 1.87	4.80*@ ± 1.00

$n = 6$.
* Significantly different from ulcer control at $p < 0.05$.
@ Significantly different from lansoprazole at $p < 0.05$.

Table 2 Curative effect of the investigated extracts on absolute ethanol-induced ulcer in rats.

Groups	Dose (mg/kg)	Lesion score (0–5)	Number of ulcers	Ulcer area (mm^2)	Ulcer index (mm)
Ulcer control	–	4.67 ± 0.52	13.32 ± 1.86	24.13 ± 1.26	18.22 ± 1.94
Lansoprazole	30	1.12* ± 0.03	1.52* ± 0.25	3.72* ± 0.07	2.34* ± 0.05
Conyza dioscoridis	125	2.24*@ ± 0.41	2.83* ± 1.33	5.20* ± 1.17	3.80*@ ± 0.98
	250	1.32* ± 0.52	1.54* ± 0.55	4.11* ± 0.89	3.11* ± 0.63
	500	1.33* ± 0.63	1.17* ± 0.83	2.70* ± 1.26	1.72* ± 0.52
Euphorbia hirta	125	2.51*@ ± 0.84	5.30*@ ± 1.63	12.21*@ ± 0.75	6.80*@ ± 1.33
	250	2.32*@ ± 0.52	4.67*@ ± 0.82	10.31*@ ± 1.37	6.20*@ ± 1.47
	500	2.20*@ ± 0.75	4.02*@ ± 1.26	8.30*@ ± 1.21	5.71*@ ± 1.21
Origanum syriacum	125	2.70*@ ± 0.52	8.33*@ ± 1.10	12.81*@ ± 1.50	9.01*@ ± 0.89
	250	2.04*@ ± 0.63	4.83*@ ± 1.17	9.20*@ ± 1.47	5.73*@ ± 1.21
	500	1.81* ± 0.75	3.00*@ ± 1.10	6.71*@ ± 2.16	4.02*@ ± 0.63
Salvia lanigera	125	2.00*@ ± 0.89	6.02*@ ± 1.10	14.00*@ ± 1.60	7.50*@ ± 0.55
	250	1.83* ± 0.08	4.33*@ ± 1.20	9.23*@ ± 1.70	4.33*@ ± 1.50
	500	1.17* ± 0.07	2.30* ± 0.80	6.71*@ ± 1.00	2.70* ± 0.70
Sisymbrium irio	125	2.20*@ ± 0.05	3.67*@ ± 0.22	11.80*@ ± 1.47	9.00*@ ± 1.26
	250	1.50* ± 0.08	2.17* ± 0.08	6.71*@ ± 0.82	4.00*@ ± 0.89
	500	1.20* ± 0.02	1.31* ± 0.05	3.70* ± 0.05	2.72* ± 0.08
Solanum nigrum	125	2.80*@ ± 0.05	3.83*@ ± 0.50	13.71*@ ± 1.50	7.20*@ ± 1.20
	250	2.00*@ ± 0.03	3.33*@ ± 0.09	9.70*@ ± 1.20	4.80*@ ± 0.80
	500	1.31* ± 0.06	2.01* ± 0.05	6.50*@ ± 0.10	2.50* ± 0.08
Solenostemma arghel	125	2.80*@ ± 0.05	7.67*@ ± 0.82	19.50*@ ± 1.38	10.00*@ ± 1.40
	250	2.30*@ ± 0.02	4.83*@ ± 1.47	11.50*@ ± 1.05	6.20*@ ± 1.33
	500	2.17*@ ± 0.09	3.50*@ ± 0.55	10.21*@ ± 1.47	5.50*@ ± 1.22

$n = 6$.
* Significantly different from ulcer control at $p < 0.05$.
@ Significantly different from lansoprazole at $p < 0.05$.

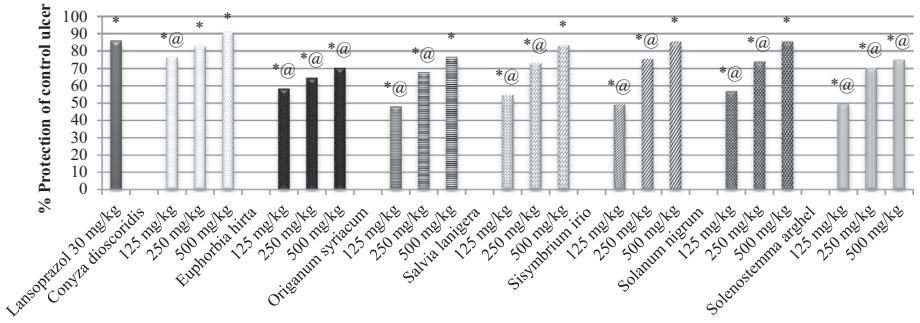

Figure 1 Prophylactic effect of investigated plant extracts on absolute alcohol-induced ulcer in rats. * Significantly different from control ulcer at $p < 0.05$. @ Significantly different from lansoprazole at $p < 0.05$.

in the gastric mucosa (Pihan et al., 1987) and scavenging these free radicals can play an appreciable role in healing these ulcers (Halliwell and Gutteridge, 2001). The antioxidant potentials of the investigated extracts may be one of the possible mechanisms by which extracts have ameliorated the ethanol-induced gastric ulceration. These results were in line with the results of many studies that correlated the antiulcerogenic activity of the extract and its antioxidant potential. Other plant extracts of *Encholirium spectabile* Mart. (Carvalho et al., 2010), *Parkia platycephala* Benth. (Fernandes et al., 2010), *Glycyrrhiza glabra* L. (Ligha and Fawehinmi, 2009) and *Carica papaya* L. (Ologundudu et al., 2008) possessed antioxidant effect in the ethanol-induced gastric damage.

3.4. Possible mechanisms of action (biochemical investigations) for the most effective extracts

Ethanol-induced gastric lesions are thought to arise as a result of direct damage of gastric mucosal cells, resulting in the development of free radicals and hyperoxidation of lipid (Terano et al., 1989). A significant decrease in the mucosal levels of non-protein sulfhydryl compounds was demonstrated in

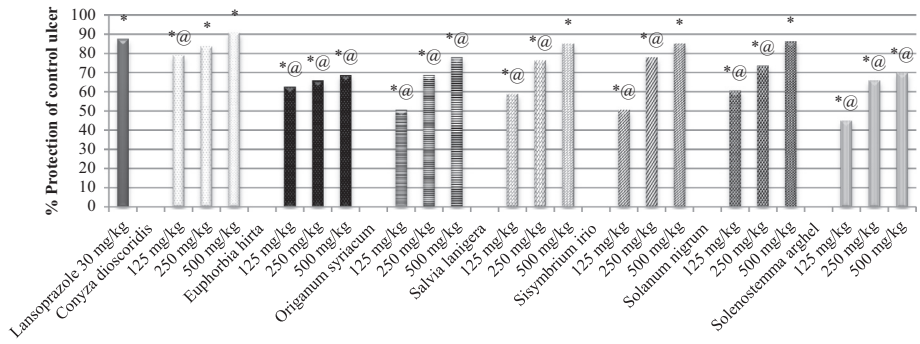

Figure 2 Curative effect of investigated plant extracts on absolute alcohol-induced ulcer in rats. * Significantly different from control ulcer at $p < 0.05$. @ Significantly different from lansoprazole at $p < 0.05$.

Table 3 Effects of the alcohol extracts of the investigated plants on scavenging DPPH radical.

Extracts	Radical scavenging activity %				
	2 mg/ml	4 mg/ml	6 mg/ml	8 mg/ml	10 mg/ml
Conyza dioscoridis	42.70 ± 1.01	79.50 ± 0.95	83.70 ± 1.00	85.80 ± 0.87	91.40 ± 1.09
Euphorbia hirta	15.20 ± 1.20	17.00 ± 1.04	19.20 ± 0.98	20.70 ± 1.01	22.10 ± 1.04
Origanum syriacum	20.20 ± 0.90	34.40 ± 1.01	42.60 ± 1.10	49.20 ± 0.90	65.60 ± 0.95
Salvia lanigera	30.50 ± 0.75	45.70 ± 0.90	50.90 ± 0.87	58.20 ± 0.84	62.30 ± 0.73
Sisymbrium irio	27.90 ± 0.98	30.10 ± 0.87	45.60 ± 1.02	49.60 ± 1.17	55.70 ± 0.99
Solanum nigrum	10.70 ± 1.07	12.40 ± 1.09	15.70 ± 1.20	17.90 ± 1.09	19.80 ± 1.20
Solenostemma arghel	22.00 ± 0.45	34.70 ± 1.21	53.90 ± 0.75	65.80 ± 1.11	85.30 ± 1.03

Table 4 Effect of *Conyza dioscoridis* and *Sisymbrium irio* on gastric thiobarbituric acid reactive substance (MDA) content on absolute alcohol-induced ulcer in rats.

Group	MDA (nmol/mg tissue)	% Change of control colitis
Normal control	50.31 ± 3.16	–
Control ulcer	92.40 ± 5.11	–
Lansoprazole 30 mg/kg	49.90* ± 7.30	46.00
Conyza dioscoridis 250 mg/kg	47.70* ± 5.50	48.38
Conyza dioscoridis 500 mg/kg	45.60* ± 6.70	50.65
Sisymbrium irio 250 mg/kg	55.20* ± 6.43	40.26
Sisymbrium irio 500 mg/kg	51.80* ± 4.30	43.94

$n = 6$.
@ Significantly different from lansoprazole at $p < 0.05$.
* Significantly different from control ulcer at $p < 0.05$.

ethanol-induced gastric damage (Szabo et al., 1981). These endogenous compounds are important for maintaining the integrity of the gastric mucosa and mediating the protective effects of prostaglandins against gastric mucosal injury (Miller and Henagan, 1984).

In the present alcohol-induced gastric ulcer model, gastric MDA content increased (92.40 nmol/mg tissue) accompanied by decreased gastric GSH content (2.02 mg/g tissue) compared to the normal rats (50.31 nmol/mg tissue and 3.52 mg/g tissue). Both *C. dioscoridis* and *S. irio* at doses 250 & 500 mg/kg produced a significant decrease in the gastric MDA content of absolute ethanol-induced ulcer rats. By comparing the percent protection from control ulcer, *C. dioscoridis* (50.6%) was more effective than both *S. irio* (43.3%) and lansoprazole (39%) (Table 4). In addition, both *C. dioscoridis* and *S. irio* at doses 250 & 500 mg/kg produced a significant enhance in the gastric GSH level of absolute ethanol-induced ulcer rats. By comparing with control ulcer, *C. dioscoridis* was more effective than both *S. irio* and lansoprazole (Fig. 3).

Furthermore, ethanol-induced gastric ulcerated rats in the present experiments showed a significant increase in serum concentrations of gastrin (200.0 pg/ml) in comparison with normal rats (78.8 pg/ml). Both *C. dioscoridis* and *S. irio* at doses 250 & 500 mg/kg produced a significant decrease in serum gastrin level of absolute ethanol-induced ulcer rats. *C. dioscoridis* was more effective than both *S. irio* and lansoprazole (Fig. 4). Gastrin is a gastrointestinal hormone that regulates gastric acid secretion, releases histamine, and regulates

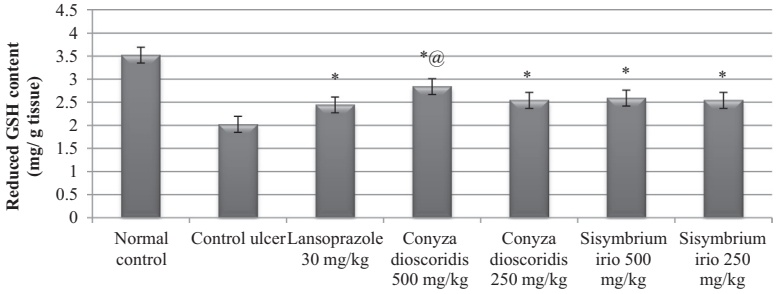

Figure 3 Effect of *Conyza dioscoridis* and *Sisymbrium irio* on gastric sulfhydryl compounds (reduced glutathione) content on absolute alcohol-induced ulcer in rats. * Significantly different from control ulcer at $p < 0.05$. @ Significantly different from lansoprazole at $p < 0.05$.

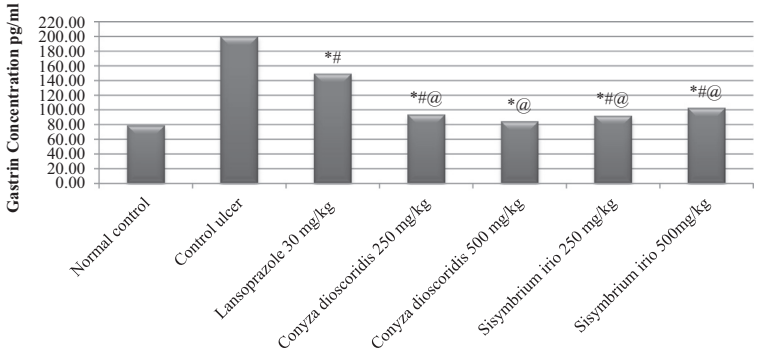

Figure 4 Effect of *Conyza dioscoridis* (L.) Desf. and *Sisymbrium irio* L. on serum gastrin level on absolute alcohol-induced ulcer in rats. *Significantly different from control ulcer at $p < 0.05$. @ Significantly different from lansoprazole at $p < 0.05$. #Significantly different from normal control $p < 0.05$.

gastric endocrine cell proliferation (Walsh, 1993). It is known that release of gastrin hormone is supplemented by acidification of the gastric lumen, which has an apparent feedback relationship between gastrin release and gastric acid secretion (Eysselein et al., 1992). The high levels of gastrin hormone in ethanol-induced ulcer model stimulate the parietal cells to hyper secrete acid, which in turn causes the gastric ulcer. The suppression of gastrin release is accompanied by the elaboration of an inhibitory antral hormone (somatostatin) that decreases gastric secretion (Mercer et al., 1997). Low intragastric pH stimulates antral D cells to release somatostatin. Somatostatin inhibits gastrin release from G cells. Reduced gastrin secretion reduces acid secretion. The antisecretory activity of both *C. dioscoridis* and *S. irio* appears to be mainly related to suppression of gastrin release. The extracts showed significant reduction in gastrin hormone release thereby decreasing the acidity of the gastric juice. These results were in harmony with the findings that, the prophylactic mechanism is based on the ability to strengthen defensive factors and the inhibitory effect on gastrin secretion (Muralidhar et al., 2009; Thirunavukkarasu et al., 2009; Ferreira et al., 2010).

An increase of pro-inflammatory cytokine level such as TNF-α has been shown in gastric and duodenal ulcers. TNF-α is involved in several physiological steps of inflammation including cell migration, edema and fever (Boraschi et al., 1998; Hwang et al., 2008; Lychkova et al., 2010). It has been proved that, TNF-α is one of the mediators that contributed to ethanol-induced ulcer (Beserra et al., 2011). When inflammation of the gastric mucosa occurs, it leads to infiltration of neutrophils and mononuclear cells that stimulates the synthesis of proinflammatory mediators including interleukin and TNF-α (Lindholm et al., 1998). The investigated extracts of *C. dioscoridis* and *S. irio* produced a significant decrease (50.47% and 48.53% change from control ulcer respectively) in the elevated plasma level of TNF-α of ethanol-induced ulcer model, and these activities were more effective than lansoprazole (44%) (Table 5). The suppression in this inflammatory mediator may be partially responsible for their activity. These findings were supported by the fact that the anti-inflammatory potential of an extract may help for its gastroprotective activity like extracts of *Gynura procumbens* (Merr.) (Mahmood et al., 2010) and *Morus alba* L. (Abdulla et al., 2009).

The active constituents of the plants under investigation may be partially responsible for their activities. Alkaloids detected in both *C. dioscoridis* and *S. nigrum* may be responsible for the antiulcerogenic activity. This is in agreement with Tan and Nyasse (2000) who reported that, alkaloids possess prophylactic antiulcerogenic activity through enhancing mucus production in addition to the antioxidant activity.

The preliminary phytochemical screening of the investigated plants revealed the presence of flavonoids, tannins, carbohydrates, sterols, proteins, and esters in addition to traces of saponins in all of the investigated plants.

Terpenoids with antiulcerogenic effects were mostly cytoprotective, and they increased the mucus production in the stomach through different mechanisms. They may enhance

Table 5 Effect of *Conyza dioscoridis* and *Sisymbrium irio* on TNF-α (Tumor Necrosis Factor- alpha) level on absolute alcohol-induced ulcer in rats.

Groups	TNF-α (pg/ml)	% protection of control ulcer
Control ulcer	12.88 ± 0.79	–
Lansoprazole 30 mg/kg	7.21* ± 0.51	44.02
Conyza dioscoridis 250 mg/kg	7.38* ± 0.41	42.70
Conyza dioscoridis 500 mg/kg	6.38*@ ± 0.38	50.47
Sisymbrium irio 250 mg/kg	9.53*@ ± 0.45	26.01
Sisymbrium irio 500 mg/kg	6.63*@ ± 0.52	48.52

$n = 6$.
* Significantly different from control ulcer at $p < 0.05$.
@ Significantly different from lansoprazole at $p < 0.05$.

Table 6 Effect of *Conyza dioscoridis* and *Sisymbrium irio* on liver and kidney functions.

Treatment	Liver function (U/l)		Kidney function (mg/dl)	
	AST	ALT	Blood urea	Serum Creatinine
Normal control	65.11 ± 2.62	144.62 ± 5.39	32.16 ± 1.83	0.36 ± 0.03
Conyza dioscoridis	62.37 ± 3.47	145.20 ± 5.51	33.50 ± 1.85	0.37 ± 0.03
Sisymbrium irio	64.50 ± 3.56	140.25 ± 4.22	35.17 ± 1.78	0.39 ± 0.02

mucosal PG content, thereby improving gastric mucosal blood flow and secretion of gastric bicarbonate and mucus which accelerates ulcer healing (Murakami et al., 1999; Ohta et al., 2005). These active compounds act as antioxidant, reduce lipid peroxides and increase the antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) in the gastric mucosa (Kim et al., 2005; Rodríguez et al., 2006). Saponins act mainly through antisecretory mechanism; they inhibit acid secretion and total acid output, and lowered the pH value of gastric juice (Lee et al., 2005).

Phenolic compounds considered one of the major families of secondary metabolites in plants; they represent a diverse group of compounds such as flavonoids, quinone, tannins and phenolic glycosides. Many phenolics exhibit antiulcerogenic activities, and they act through different mechanisms. Antisecretory effect was reported for phenolic glycosides (Carvalho et al., 2007; Severi et al., 2009), while quinones act as cytoprotective (Lee et al., 2010), by increasing PG synthesis.

Flavonoids are important for the normal growth, development and defense of plants. They possess both cytoprotective and antisecretory activities. They exert a gastroprotective action in mammals by increasing endogenous prostaglandin levels, decreasing histamine secretion, inhibiting *Helicobacter pylori* and scavenging oxygen derived free radicals. Their antisecretory mechanism includes the antioxidant property (Lastra et al., 1994; Martin et al., 1998; Coelho et al., 2006; Olaleye and Farombi, 2006).

3.5. Sub-chronic toxicity

The non-toxic nature of the investigated extracts in acute toxicity study is well supported by the results of sub-chronic toxicity study. Oral dosing of *C. dioscoridis* and *S. irio* extracts to rats in a dose of 500 mg/kg for 35 days did not show any significant effect on the levels of ALT, AST, urea and creatinine in their sera as compared to control (Table 6).

The serum transaminase level is most widely used as a measure of hepatic injury, due to its ease measurement and high degree of sensitivity. It is useful for the detection of early damage of hepatic tissue. Since the activity of ALT and AST is specific assayable liver enzymes, their normal levels in serum of rats treated for 35 days means that the alcohol extracts of *C. dioscoridis* and *S. irio* are not hepatotoxic.

Urea and creatinine are the most sensitive biochemical markers employed in the diagnosis of renal damage. In kidney damage, there will be retention of urea and creatinine in the blood (Nwanjo et al., 2005); therefore, marked increase in serum urea and creatinine is the indication of functional damage to the kidney (Panda, 1999). By these indicators, the alcohol extracts of *C. dioscoridis* and *S. irio* are therefore, not nephrotoxic in rats.

4. Conclusion

All the investigated plants showed potent anti-ulcerogenic and antioxidant activities in a dose dependent manner. The antisecretory activity of both *Conyza dioscoridis* and *Sisymbrium irio* appears to be mainly related to the suppression of gastrin release. In addition, the antioxidant potentials of the extracts were well supported with the reduction of gastric MDA and enhancing the level of reduced GSH. Suppression of the inflammatory mediator TNF-α may be one of the possible mechanisms of action of the investigated extracts. The total alcohol extracts of *Conyza dioscoridis* and *Sisymbrium irio* are non-toxic and showed no alteration on liver and kidney functions.

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