

Evaluation of Selected Desert Plants as Anti-ulcerogenic Natural Products

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Abstract: The antiulcerogenic activity of the total alcohol extracts of five desert plants *Alhagimurarium* Medic. Leguminosae; *Cissusquadrangularis* Linn. Vitaceae; *Cocciniagrandis* L. Cucurbitaceae; *Convolvulus arvensis* L. Convolvulaceae and *Schouwiathebaica* Webb. Cruciferae were studied, for each extract three doses (125, 250 and 500 mg/kg) were tested. Two models are used in this study; alcohol-induced ulcer and pyloric ligation in rats. Phytochemical screening and acute toxicity were studied. The extracts possessed anti-ulcerogenic activity in a dose dependent manner (125 to 500 mg/kg) with different potentials in both models. In both models the extract of *Cocciniagrandis* at dose 500 mg/kg was the most effective one and the lower activity was for *Schouwiathebaica*. In alcohol-induced ulcer model, *C. grandis* produced protection from control by 91.2 % while *S.thebaica* produced 57.7 %. In the pyloric ligation model, all extracts can decrease ulcer index, gastric juice volume and total acidity with different percentage 84.2 for *C.grandis* to 41.8% for *S.thebaica*. No toxicity signs were observed for the extracts up to 5 g/kg all plants under investigation possessed good anti-ulcerogenic activity in a dose dependent manner. The mechanism of the anti-ulcerogenic activity included both cytoprotective and anti-secretory. Flavonoids and terpenoids could be partially responsible for the activity of most of the selected plants.

Key words: Peptic ulcer, flavonoids, pyloric ligation, *Cissusquadrangularis*, *Cocciniagrandis*.

INTRODUCTION

Peptic ulcer disease (PUD) is considered as one of the most common disorders worldwide. It develops when there is an imbalance between the damaging and defensive factors at the luminal surface of the epithelial cells.

Aggressive factors include *Helicobacter pylori*, HCL, pepsins, NSAIDs (non steroidal anti-inflammatory drugs), bile acids, Ischemia and hypoxia, smoking and alcohol. While defensive factors include bicarbonate, mucus layer, prostaglandins (PGs) and growth factors (Harlodet *et al.*, 2007). Many synthetic drugs were used in treatment of peptic ulcer they may reduce stomach acid secretion (antiacids), protect the mucus layer of the stomach (Demulcents) or eliminate *Helicobacter pylori*. But incidence of relapses and adverse effects of synthetic drugs are major problems (Katzung, 2004; Waller *et al.*, 2005).

A widespread search has been launched to identify new antiulcer therapies from natural sources. Plants have been used for thousands of years as a remedy and they are considered being a potential source to control various diseases including gastric ulcer.

Alhagimaurorum was reported in folk medicine to treat various types of gastrointestinal discomfort, liver disorders, rheumatic pains, bilharziasis and urinary tract infection (Bulus, 1983). It possesses anti-inflammatory, analgesic activities (Awaad *et al.*, 2011) and anti-diarrheal activity (Atta and Mounier, 2004).

Cissusquadrangularis is a plant in the grape family that is used to treat many conditions. It was found to be effective in the management of obesity (Hasani-Ranjbar *et al.*, 2009). It is used in treatment of hemorrhoid due to its analgesic and anti-inflammatory activities as well as the venotonic effect (Panthong *et al.*, 2007). It possesses anti-osteoporotic activity (Potu *et al.*, 2010). It was reported to be used against schistosomiasis in Mali (Bah *et al.*, 2006) and hepatoprotective effect which might be attributed to its antioxidant property (Viswanatha *et al.*, 2010).

Cocciniagrandis possesses antidiabetic activity (Singh *et al.*, 2007), antimicrobial activity (Farrukh *et al.*, 2008). *Convolvulus arvensis* was described as a purgative and fever-reducer in Greek folk medicine. It is still used in Turkey as a vegetable and condiment; in Arabic-speaking areas, the roots and leaves are still used as an anti-hemorrhagic and laxative (Austin, 2000).

Schouwiathebaica has been shown to possess antinociceptive effect (Atta and Abo El Sooud, 2004), antidiarrhoeal effect (Atta and Mounier, 2005) and hepatoprotective activity (Awaad *et al.*, 2006).

MATERIAL AND METHODS

Plant Material:

The aerial parts of *Alhagimurarum* Medic. (Leguminosae), *Cissusquadrangularis* Linn. (Vitaceae), *Cocciniagrandsis* L. (Cucurbitaceae), *Convolvulus arvensis* L. (Convolvulaceae) and *Schouwiathebaica* Webb (Cruciferae) were collected from deserts of Saudi Arabia during the spring of 2011 and kindly identified by Dr. Jacob T. Pandalayil (Assistant Professor of Plant Taxonomy, Botany and Microbiology Department, Faculty of science, King Saud University) and compared with the published plant description (Migahid, 1996). A voucher specimens have been deposited in the herbarium of faculty of Sciences, King Saud University. Collected plant material was shade dried, reduced to fine powder, packed in tightly closed containers and stored for further studies.

Animals:

Healthy adult male Wistar rats (150-180 g) and Albino mice (20-22 g) were purchased from the animal house of King Saud University. Animals were housed in standard polypropylene cages with wire mesh top and fed a standard pellet diet with water *ad libitum* pens and water bottles were mounted outside the cages. The cages were washed once a week. Animals were maintained under standard laboratory conditions on a 12 h light/dark cycle in a temperature-controlled room at $21 \pm 3^\circ\text{C}$.

Phytochemical Screening:

Powdered samples of the aerial parts of each plant were separately subjected to preliminary phytochemical screening according to the published methods (Trease & Evance, 2002; Sofowora, 1993; Harborne, 1973).

Identification of carbohydrates was done using both Molisch's and Fehling's tests. For alkaloids, Mayer's test was used. Froth test was used for saponins. For sterols and terpenes, Libermann-Burchard test and Salkowski's tests were used. Proteins and amino acids were identified using ninhydrin reagent. While buljet reagent was used for cardenolides.

Extraction:

The air dried powder of *A.murarum*, *C.quadrangularis*, *C. grandis*, *C.arvensis* and *S.thebaica* aerial parts (1 kg, each) were extracted by percolation in 90% ethanol (Awaad *et al.*, 2011) at room temperature for two days. The ethanol extract was filtered and the residues were re-percolated for four times. The total ethanol extract was concentrated under reduced pressure at a temperature not exceeding 35°C to yield a dry extract of 194, 210, 165, 193 and 178 g for *A.murarum*, *C.quadrangularis*, *C. grandis*, *C.arvensis* and *S.thebaica* respectively.

Preparation of the Extracts for Biological Studies:

The total ethanol extracts of *A.murarum*, *C.quadrangularis*, *C. grandis*, *C.arvensis* and *S.thebaica* were suspended separately in distilled water (vehicle) by the aid of Tween 80.

Acute Toxicity Test:

Mice were fasted overnight (only provided water). Plant extracts were administered orally to the groups at the dose level of 10 mg/kg and observed for 48 h for mortality. If no mortality was observed, the procedure was repeated for further higher doses such as 100, 1000 and 5000 mg/kg body weight. Toxic symptoms such as behavioral changes, motor reflexes and mortality were observed for 48 hours (Ecobichon, 1997).

Antiulcerogenic Activity:

Two models are used in this study:

1. Alcohol-induced gastric lesions for evaluating the cytoprotective mechanism (Ranitidine as a standard drug).
2. Pylorus ligated rats for evaluation of the antisecretory mechanism (Omeprazole as a standard drug).

Alcohol-Induced Gastric Lesions:

Groups of rats (each of 6) were fasted for 24 h (Gargeet *et al.*, 1993). The 1st group was kept as sham group, while the 2nd one was kept as control, both groups administered water orally. Groups 3rd to 17th received oral alcohol extracts of *A.murarum*, *C.quadrangularis*, *C. grandis*, *arvensis*, *S.thebaica* at doses of 125, 250 and 500 mg/kg respectively. The last group of rats was given ranitidine orally (as standard drug) in a dose of 100 mg/kg. For each group, two doses were given in the first day at 08:00 and 16:00 clock; a third dose was given on the second day 1.5 h before induction of gastric ulceration. All rats except the normal control were given 50% ethanol in distilled water (v/v) in a dose of 10 ml/kg orally to induce gastric ulceration. One hour after ethanol administration, all rats were killed and the stomachs were rapidly removed, opened along their greater curvature. The % protection was determined according to the formula, where lesion index is the sum of the total length of ulcers in each group divided by its number.

$$\% \text{ Protection} = \frac{(\text{Control ulcer index}) - (\text{Test ulcer index})}{(\text{Control ulcer index})} \times 100$$

Pylorus Ligated Rats:

Total alcohol extract of *A.murarium*, *C.quadrangularis*, *C. grandis*, *C.arvensis* and *S.thebaica* (125, 250 and 500 mg/kg), omeprazole (20 mg/kg) and water were orally administered for 7 successive days to rats. On day 7, after the last dose, the rats were kept for 24 h fasting. The abdomen was opened under light ether anesthesia and pylorus was ligated (without causing any damage to its blood vessels). Then the stomach was replaced carefully and the abdominal wall was closed with interrupted sutures. During the postoperative period; animals were deprived of water (Shay *et al.*, 1945). Stomachs were dissected out and contents were collected into clean tubes after 4 h from ligation. Many parameters were determined; volume, pH, free and total acid content of gastric juice (Kulkarni, 1999). In addition, stomachs were opened along the greater curvature and examined for ulcers. Like the method mentioned before, the ulcer index was evaluated.

Determination of Acidity:

Centrifuged and filtered gastric secretion (1ml) was titrated against 0.1N sodium hydroxide; for determination of free acidity Topfers reagent was used as indicator and for determination of combined acidity 1% phenolphthalein was used as indicator. The sum of the two titrations was total acidity (Parmar *et al.*, 1984) and expressed as mEq/l.

$$\text{Acidity} = \text{Volume of NaOH} \times \text{Normality of NaOH} \times 100 / 0.1 \text{ mEq} / \text{L}.$$

Statistical Analysis:

Statistical analysis was carried out using one-way ANOVA test (Kuchl, 1994).

RESULTS AND DISCUSSION

Phytochemical Screening:

All plants contain flavonoids, terpenoids, esters, tannins, proteins and glycosides (Table 1).

Table 1: Chemical constituents of plants under investigation.

Constituents	<i>A.m.</i>	<i>C.a.</i>	<i>C.g.</i>	<i>C.q.</i>	<i>S.t.</i>
Alkaloids and/or nitrogenous bases	-	+	+	+	-
Anthraquinones	-	-	-	-	-
Carbohydrates and/or glycosides	+	+	+	+	+
Cardinolides	-	-	-	-	-
Flavonoides	+	+	+	+	+
Lactones and/or esters.	+	+	+	+	+
Proteins and/or amino acids	+	+	+	+	+
Saponins	±	±	±	±	±
Tannins	+	+	+	+	+
Unsaturated sterols and/or triterpenes	+	+	+	+	+

(*A.m.*) *Alhagimurarium*, (*C.a.*) *Convolvulus arvensis*, (*C.g.*) *Cocciniagrandsis*, (*C.q.*) *Cissusquadrangularis* and (*S.t.*) *Schouwia thebaica*, (+) present, (-) absent and (±) traces.

Acute Toxicity Test:

No morbidity or mortality was recorded in mice treated with any of the tested extract at doses up to 5 g/kg. Therefore, the tested plant can be categorized as highly safe since Buck *et al.*, (1976) reported that, substances possessing LD50 higher than 50 mg/kg are nontoxic.

Alcohol-Induced Gastric Lesions:

Ethanol administered orally to rat produced characteristic lesions in the glandular portion of the stomach, these lesions appeared as elongated bands of thick, black and dark red lesions. The total alcohol extract of the investigated plants produced a significant protection in a dose dependent manner with different potentials. The most active extract among the tested plants is *Cocciniagrandsis* at dose 500 mg/kg (91.2%) and the lower activity is for *Schouwia thebaica* at dose 125 mg/kg (29.5%) in comparison to control, ranitidine as reference standard drug makes reduction of ulcer 51.8% (Table 2).

Ethanol induced gastric ulcer model was used to evaluate the cytoprotective effect of the extracts. Formation of gastric lesion induced by ethanol may be due to enhance in gastric blood flow which leads to the development of the haemorrhage and necrosis. In addition, alcohol penetrates gastric mucosa causing damage of cell and plasma membrane which leads to increase in the permeability of intra cellular membrane to sodium and water. Furthermore, the massive intracellular accumulation of calcium represents a major step in the

pathogenesis of gastric mucosal injury. This leads to cell death and exfoliation in the surface epithelium (Soll, 1990; Surendra, 1999).

Pylorus Ligated Rats:

In pyloric ligation induced ulcer model, Oral administration of the investigated extracts in different dose showed significant reduction in ulcer index, gastric volume, total acidity as compared to control. The percent of protection was ranged from 84.2 to 41.8% for *Cocciniagrandis* (500 mg/kg) and *Schouwiatehaica* (125 mg/kg) respectively whereas it was 77.9% for Omeprazole (20 mg/kg) (Table 3). Furthermore, gastric volume and total acidity were decreased and PH was increased by all of the tested extract by different percentage. *Cissusquadrangularis* and *Cocciniagrandis* at doses 250 and 500 mg/kg were more effective than the standard drug Omeprazole.

Table 2: Effect of extracts of plants under investigation on absolute alcohol-induced ulcer rats.

Treatment	(Dose mg/ kg)	Ulcer index	% Protection
Control	0	17.02±1.12	0
<i>Alhagimurarum</i>	125	11.97±1.41*	29.7
	250	8.8±1.50**	48.3
	500	6.5±1.22**	61.8
<i>Convolvulus arvensis</i>	125	5.54±0.99**	67.4
	250	4.3±1.06**	74.7
	500	2.9±0.93**	82.9
<i>Cocciniagrandis</i>	125	3.97±0.88**	76.7
	250	2.8±1.12**	83.6
	500	1.5±0.95**	91.2
<i>Cissusquadrangularis</i>	125	10.0 ± 0.15*	41.3
	250	7.9 ± 1.3**	53.6
	500	5.9 ± 0.86**	65.3
<i>Schouwiatehaica</i>	125	12.0 ± 0.53*	29.5
	250	9.7 ± 0.69*	43.0
	500	7.2 ± 1.2**	57.7
Rantidine	100	8.20 ± 0.80**	51.8

Values are mean ± SE, n=6;

** Significantly different from control *p < 0.05, **p < 0.01.

The ligation of the pyloric end of the stomach causes accumulation of gastric acid in the stomach. The increase in the gastric acid secretion causes stomach ulcers. This model produced lesions located in the lumen region. The alcohol extracts and Omeprazole significantly decreased the total acidity; this suggests that it having an antisecretory effect.

The extract shows protection against characteristic lesions produced by ethanol and pyloric ligation, this antiulcer effect may be due to both reductions in gastric acid secretion and increase gastric cytoprotection.

Table 3: Effect of extracts of plants under investigation on different parameters on pyloric ligated rats.

Treatment	Dose (mg/ kg)	Ulcer index	% Protection	PH of gastric juice	Gastric juice volume (ml)	Total acidity mEq/l
Control	0	15.8± 1.1	0	2.4±0.2	8.9±0.18	120.5± 0.24
<i>Alhagimurarum</i>	125	8.5±1.09**	46.1	2.6±0.18	6.1±0.12	83.4±0.83
	250	7.1±1.2**	55.1	3.1±0.13*	4.8±0.15**	75.9±0.37*
	500	5.2±0.89**	67.1	3.9±0.25**	3.5±0.29**	68.6±0.25*
<i>Convolvulus arvensis</i>	125	6.1±2.1**	61.4	3.3±0.17*	5.1±0.18*	71.8±0.82*
	250	4.1±1.11**	74.1	3.8±0.15**	3.4±0.15**	65.5±1.1*
	500	2.8±0.95**	82.3	4.5±0.2**	2.5±0.23**	59.3±0.94**
<i>Cocciniagrandis</i>	125	4.6±1.15**	70.9	3.7±0.18**	4.4±0.21*	67.5±0.51*
	250	3.4±1.2**	78.5	4.5±0.15**	3.1±0.18**	60.1±0.13**
	500	2.5±0.95**	84.2	4.9±0.2**	2.2±0.22**	55.2±0.29**
<i>Cissusquadrangularis</i>	125	6.3±0.18**	60.1	2.7±0.19	5.5±0.12	75.8±1.2*
	250	5.5±2.2**	65.2	3.5±0.31**	3.9±0.17**	69.1±0.25*
	500	3.2±1.7**	79.8	4.3±0.22**	2.7±0.24**	62.9±0.15**
<i>Schouwiatehaica</i>	125	9.2±0.28**	41.8	2.5±0.23	6.9±0.13	91.3±0.22
	250	7.5±0.88**	52.5	3.1±0.19*	5.5±0.19	85.4±0.98
	500	6.8±1.12**	60	3.6±0.25**	3.7±0.26**	78.2±0.29*
Omeprazole	20	3.5±0.82**	77.9	4.8±0.16**	2.5±0.19**	58.2±0.18**

Values are mean ± SE, n=6;

** Significantly different from control *p < 0.05, **p < 0.01.

Chemical investigation of the tested plants revealed that the main active constituents are flavonoids and terpenoids. Flavonoids are important for the normal growth, development and defense of plants. Flavonoids

possess both cytoprotective and antisecretory activities. They increase endogenous prostaglandin levels, decrease histamine secretion, and scavenging oxygen derived free radicals (Coelho *et al.*, 2006, Martin *et al.*, 1998, Lastra *et al.*, 1994, Olaleye & Farombi, 2006).

In addition, terpenoids with antiulcerogenic effects are mostly cytoprotective, they increase the mucus production in the stomach through different mechanisms, among these are; it enhanced mucosal PG content, thereby improving gastric mucosal blood flow and secretion of gastric bicarbonate and mucus which accelerates ulcer healing (Ohta *et al.*, 2005 & Murakami *et al.*, 1999).

The gastro protective mechanism is based on the ability to strengthen defensive factors like prostaglandin synthesis, in addition to other gastro protective actions (Ferreira *et al.*, 2010). The participation of the antioxidant mechanisms on the gastro protective effects prevents the oxidative damage of gastric mucosa by blocking lipid peroxidation and by significant decrease in superoxide dismutase, and increase in catalase activity (Carvalho *et al.*, 2010; Almeida *et al.*, 2011). Furthermore, the anti-inflammatory potentials of an extract may help its gastro protective activity (Mahmood *et al.*, 2010; Abdulla *et al.*, 2009).

Conclusion:

We could conclude that, all plants under investigation possessed good antiulcerogenic activity in a dose dependent manner. The mechanism of the antiulcerogenic activity included both cytoprotective and antisecretory. Flavonoids and terpenoids could be partially responsible for the activity of most of the selected plants.

ACKNOWLEDGMENT

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for the work through the research group project NO RGP-VPP-060.

Declaration of Interest:

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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