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Zataria multiflora Boiss. essential oil against ethanol-induced gastric ulcer in rats by antioxidant properties and increase in nitric oxide production

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ABSTRACT

Introduction: The present study investigated protective effect of *Zataria multiflora* essential oil on ethanol-induced gastric ulcer in rats along with its possible mechanism(s).

Methods: Eighty male adult rats were randomly allocated into 8 groups as follows: 1: negative control (NC); 2, 3 and 4: positive control (PC, distilled water), vehicle control (VC, corn oil) and comparative control (CC, omeprazole 20 mg/kg in distilled water), respectively; 5, 6, 7 and 8: treated with 100, 200, 400 and 800 µL/kg *Z. multiflora* essential oil. After 1 hour, gastric ulcer was induced by 4 mL/kg 75% ethanol orally to rats of groups 2-8. One hour later, blood samples were collected and then all rats were sacrificed and their stomachs were immediately removed.

Results: In PC and VC groups severe lesions were observed in stomachs where mucosal lesions in CC group as well as groups treated with *Z. multiflora* essential oil (especially higher doses) were very mild with regard to ulcer area and number. No significant difference was observed in mucosal prostaglandin E2 (PGE2) and serum tumor necrosis factor-α (TNF-α) level among groups, gastric mucosal nitric oxide (NO) content was significantly higher in rats treated with *Z. multiflora* essential oil at 200, 400 and 800 µL/kg as compared to PC group. Rats in CC, *Z. multiflora* 400 and *Z. multiflora* 800 groups showed higher mucosal total antioxidant capacity (TAC) as compared to PC group.

Conclusion: *Z. multiflora* essential oil has a gastro-protective effect against ethanol-induced gastric ulcer in rats which is probably due to its antioxidant and NO production enhancing effect.

Implication for health policy/practice/research/medical education:
The present study paves the road for further investigations on protective potential of *Z. multiflora* essential oil against gastric ulcers with different aetiologies and its plausible use as an herbal agent in such diseases.

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Introduction

Peptic ulcer is a common gastrointestinal disease in the world (1). Peptic ulcers are sites of loss of continuity of part of the wall of organs of the gastrointestinal tract exposed to the gastric chloridopeptic secretion. The organs affected are more frequently the stomach and the duodenum (2).

When aggressive factors like *Helicobacter pylori*, HCl, pepsin, nonsteroidal anti-inflammatory drugs, bile acids, etc. conquer defensive factors including bicarbonate, mucus layer, mucosal blood flow, prostaglandins and growth factors; peptic ulcers are anticipated (3).

Ethanol is a risk factor for developing gastric ulcers. Different mechanisms are proposed for ethanol-induced gastric ulcers among them is that ethanol solubilizes protective mucus layer on gastric epithelial cells and make them very vulnerable to HCl and pepsin secreted to the gastric lumen (4). Induction of oxidative stress is another mechanism that plays a role in ethanol-associated gastric ulcers (5-7). Microcirculatory disruption may also be important (8).

The severe detrimental influence of ethanol on gastric mucosal integrity has been exploited for establishment of ethanol-induced gastric ulcer model in laboratory animals

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which has been successfully used by different investigators and now is a routine model of this disease. In contrast with some other models of gastric ulcers like pylorus ligation (Shay rats), this model does not rely on gastric acid secretion (9). Therefore, this model is particularly advised for evaluating agents that have cytoprotective and/or antioxidant activities (1).

Although different pharmaceutical preparations are available to relieve clinical manifestations of gastric ulcers and can considerably slow down or even totally stop the process of ulcer development, side effects due to these drugs can adversely affect their routine or long-term use and reduces the patient's compliance. Herbal remedies with a history of use by native people in different parts of the world present a promising opportunity in this regard.

Zataria multiflora Boiss. is a thyme-like plant belonging to the Lamiaceae family that geographically grows wild only in central and southern Iran, Pakistan and Afghanistan (10). Not only a popular food condiment, *Z. multiflora* is also well-known for its diverse beneficial effects including antinociceptive, antimicrobial, spasmolytic, anti-inflammatory and antioxidant properties (11) as well as treatment of some gastrointestinal disorders like bloating, dyspepsia and irritable bowel syndrome (12). Essential oil of this plant with oxygenated monoterpenes as the major constituent is mostly addressed for the biological effects (10).

Although in folk medicine *Z. multiflora* has been used in treatment of gastrointestinal problems, we could not find any published data on plausible effect of this plant on gastric ulcer. This motivated us to investigate the effect of *Z. multiflora* essential oil on ethanol-induced gastric ulcer in rats along with its possible protective mechanism(s).

Materials and methods

Determination of essential oil chemical composition

Essential oil of *Z. multiflora* prepared by hydro distillation method was purchased from Barij Essence Pharmaceutical Co., Kashan, Iran. Phytochemical analysis of the essential oil was performed by gas chromatography/mass (GC/MS) spectrometric method by Varian 3400-Varian Saturn II GC/MS system, Canada. A DB-5 column (30 m length × 0.25 mm i.d., film thickness 0.25 µm) was used. The column temperature was set at 60-250°C with 3°C increases per minute. Injector port temperature was 260°C and carrier gas was helium at a flow rate of 31.5 cm/s. Ionization voltage of mass spectrometer and ionization source temperature were 70 eV and 270°C, respectively.

Identification of individual compounds was based on Kovats or retention indices relative to retention times of normal hydrocarbons (C7-C25) and comparing them and their mass spectra with those of authentic samples or with available library data of the GC/MS system and Adams libraries spectra (13).

Animals and study design

Eighty male Wistar adult rats were acclimatized for a week to environmental conditions including feeding with commercial pellets *ad libitum*, tap water and ambient temperature of around 23°C and 12/12 light/dark cycle. Then rats were randomly allocated into 8 equal groups and treated as follows: group 1 rats were considered as negative control (NC) group and did not receive any treatment during the experiment; rats in groups 2, 3 and 4 were considered as positive control (PC, distilled water), vehicle control (VC, corn oil as the vehicle for *Z. multiflora* essential oil) and comparative control (CC), omeprazole (Abidi pharmaceutical Co., Iran), 20 mg/kg in distilled water (the dose was chosen according to a previous study) (14). Groups 5, 6, 7 and 8 were treated with 100, 200, 400 and 800 µL/kg *Z. multiflora* essential oil. All different substances were administered by oral gavaging, 1 hour before induction of gastric ulcer and volume of administration kept the same for rats with identical weight in different groups. Gastric ulcer induction was performed by oral administration of 4 mL/kg 75% ethanol (15) to rats of groups 2-8. One hour after ethanol administration, blood collection from all rats was performed under ether anesthesia by cardio centesis and then all rats were sacrificed by deepening anesthesia and stomachs were immediately removed.

Procedures used in the present study are in accordance with institutional ethical guidelines for use of animals in experiments which are compatible with European convention for the protection of vertebrate animals used for experimental and other scientific purposes.

Determination of number and area of gastric ulcers

Stomachs were opened by an incision through greater curvature and after rinsing with phosphate buffer solution photographs were made and glandular part of the stomachs was evaluated for the presence of ulcers. Long hemorrhagic lesions in mucosa were considered as ulcers. Numbers of ulcers were counted and then ulcer area was calculated by Planimetric method (16) using Axio Vision LE software. Stomachs were kept in -70°C until further use.

Determination of nitric oxide content, total antioxidant capacity and prostaglandin E2 of gastric mucosa

Glandular part of the stomach was homogenized in phosphate buffer solution pH = 7.4 (100 mg/mL) and after centrifugation at 5000 g in 4°C for 5 minutes the supernatant was used for determination of NO content as well as total antioxidant capacity (TAC) by colorimetric methods. Kits were prepared by Biocore Diagnostik (ZellBio), Germany and assays were performed as described in manufacture's guidelines.

Samples used for PGE2 assay passed two freeze-thaw cycles before centrifugation and determination of PGE2 content in supernatant was performed by ELISA method using Cusabio, rat PGE2 ELISA kit, China.

Determination of tumor necrosis factor-α in serum

Blood samples were centrifuged at 3000 rpm for 10 minutes and harvested sera were stored in -70°C. TNF-α assay was performed on sera by using Biorbyt's rat TNF-α

ELISA kit, UK.

Data analysis

Data were presented as mean ± SD and all comparisons were made by analysis of variance (ANOVA) method followed by Tukey multiple comparison test as the post hoc. A $P < 0.05$ was considered as the significant level.

Results

Chemical composition of essential oil

Different constituents of the essential oil are summarized in Table 1. Thymol and carvacrol were major constituents each comprising more than 30% of the essential oil, followed by p-cymene with 9.5%.

Gross evaluation of gastric glandular mucosa and number and area of ulcers

As shown in Figure 1, administration of ethanol to rats of positive and vehicle control groups resulted in severe hyperemia and obvious hemorrhagic lesions in stomachs which were considered as ulcers. Mucosal lesions in comparative control group as well as groups treated with *Z. multiflora* essential oil (especially higher doses) were very mild. This observation was reflected in the values of total ulcer area and number in stomachs of rats in different groups where groups 2 and 3 had significantly higher values as compared to other groups. Data are summarized in Table 2.

NO, TAC, PGE2 content of gastric mucosa and serum TNF-α level

As shown in Figure 2, although there were no significant differences among groups in mucosal PGE2 and serum TNF-α levels, gastric mucosal NO content was significantly higher in rats treated with *Z. multiflora* essential oil at 200, 400 and 800 µL/kg as compared to PC group with P value of 0.006 for *Z. multiflora* 200 and $P < 0.001$ for *Z. multiflora* 400 and 800 groups. Gastric NO contents of rats in Z. multiflora 100 and CC groups were statistically the same and showed a slight increase as compared to PC. Another significantly changed parameter was TAC that showed the highest increase in rats of CC, *Z. multiflora* 400 and *Z. multiflora* 800 as compared to PC group with $P < 0.001$ for all comparisons. Although gastric mucosal TAC of rats in *Z. multiflora* 100 and *Z. multiflora* 200 groups was lower than CC, *Z. multiflora* 400 and *Z. multiflora* 800 it showed a significant increase as compared to PC group ($P = 0.032$ and $P = 0.004$, respectively).

Table 1. Phytochemical analysis of *Z. multiflora* essential oil

Compound	%	Kovats indices
α –thujen	0.261	930
α –pinene	3.275	940
Comphen	0.183	954
β –pinene	0.437	980
3-octanone	0.345	987
Myrcene	0.901	992
α –terpinene	1.796	1020
p –cymene	9.575	1026
Limonene	0.384	1032
1.8- cineole	0.571	1035
γ –terpinene	5.413	1064
Terpinolene	0.204	1088
Linalool	1.232	1100
terpinene-4-ol	0.696	1178
α –terpineol	0.761	1190
methyl ether thymol	0.957	1237
methyl ether carvacrol	1.393	1245
Thymol	34.670	1292
Carvacrol	32.070	1300
thymol acetate	0.786	1355
carvacrol acetate	0.991	1373
e –caryophylene	1.840	1418
aromadendroene	0.763	1430
viridiflorene	0.493	1495
Total	100	

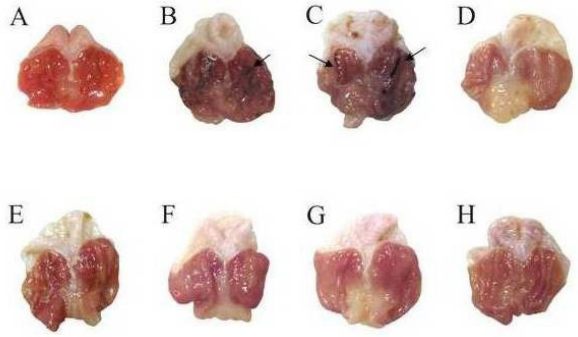

Figure 1. Representative gastric mucosae of rats in different groups. A: negative control; B: positive control; C: vehicle control; D: comparative control (omeprazole) and E, F, G and H: *Z. multiflora* essential oil at 100, 200, 400 and 800 µL/kg by oral gavaging. Ulcerative lesions are shown by arrows.

Table 2. Total ulcer area and number/stomach (mean ± SD) in different groups

Parameter	Groups							
	Negative control	Positive control	Vehicle control	Comparative control	ZMEO 100 µL/kg	ZMEO 200 µL/kg	ZMEO 400 µL/kg	ZMEO 800 µL/kg
Total ulcer area (mm^2/ stomach)	0.00 ± 0.00[a]	21.38 ± 1.56[b]	19.25 ± 3.67[b]	1.19 ± 0.54[a]	1.02 ± 0.51[a]	0.29 ± 0.10[a]	0.13 ± 0.09[a]	0.12 ± 0.08[a]
Total number of ulcers/stomach	0.00 ± 0.00[a]	7.33 ± 1.07[b]	6.22 ± 0.98[b]	1.90 ± 0.46[a]	1.30 ± 0.60[a]	0.89 ±0.26[a]	0.37 ±0.26[a]	0.40 ±0.30[a]

Abbreviation: ZMEO: *Zataria multiflora* essential oil.
Different superscript letters are used to show significant differences in a row ($P < 0.05$).

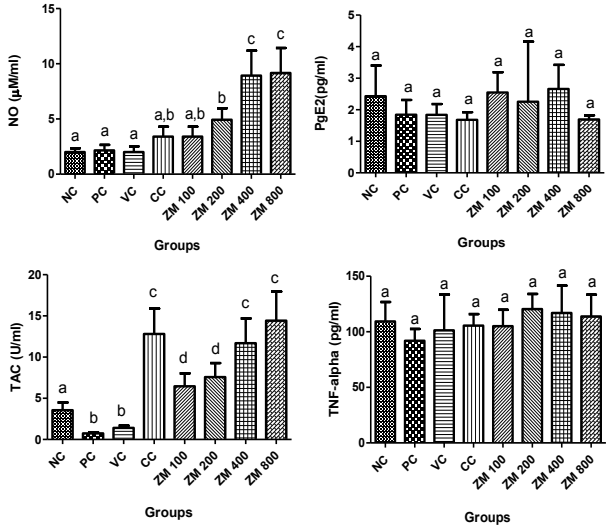

Figure 2. NO (A), TAC (B), PGE2 content of gastric mucosa (C) and serum TNF-α (D) of rats in different groups. Data are presented as mean ± SD. Significant differences among groups are indicated by different letters ($p<0.05$). NC: negative control; PC: positive control; VC: vehicle control; CC: comparative control (omeprazole) and *Z. multiflora* 100, *Z. multiflora* 200, *Z. multiflora* 400 and *Z. multiflora* 800: *Zataria multiflora* essential oil at 100, 200, 400 and 800 µL/kg by oral gavaging.

Discussion

Herbal products have always had a special place in treatment of gastrointestinal disorders and their role is getting even more pronounced with regard to outcomes of modern studies. *Zataria multiflora* is an aromatic medicinal plant, with a history of use in different diseases especially in the form of essential oil. In 2010, Saei-Dehkordi et al, evaluated chemical composition of *Z. multiflora* essential oil obtained from different parts of Iran by GC/MS method (17). The authors found 34, 34, 32, 29 and 53 various compounds in essential oils prepared from *Z. multiflora* of five different geographical origins and reported that main components identified from different samples, were almost the same with thymol as the most abundant compound which is consistent with our study. These authors also showed that all essential oils had a remarkable antioxidant activity, a fact that has been confirmed by other researchers (18,19).

In ethanol-induced gastric ulcer, oxidative stress has a pivotal role in generation of necrotic lesions. In fact, disruption of the mucus-bicarbonate barrier and cell rupture in the wall of blood vessels are probably due to lipid peroxidation, formation of free radicals and intracellular oxidative stress (20). In our study, amelioration of gastric ulcers by different doses of *Z. multiflora* essentials oil was accompanied by higher mucosal TAC with better preventive outcome and more mucosal TAC in groups treated with higher doses. On the other hand, omeprazole administration also resulted in TAC elevation similar to that of *Z. multiflora* 400 and *Z. multiflora* 800 µL/kg. Omeprazole is commonly administered in patients with gastric ulcer due to its strong effect on suppressing gastric acid secretion. As previously stated elsewhere in the text, omeprazole as the comparative control almost completely protected gastric mucosa from ethanol-induced lesions, however acid secretion does not have an appreciable role in generation of ulcers in ethanol-induced gastric ulcer model (9). Conversely, in 2003 Biswas et al, clearly showed that a major part of gastro protective property of omeprazole is related to its potent antioxidant activity, a fact that is consistent with the outcome of our study (21).

Another parameter that was significantly increased in rats treated with 200, 400 and 800 µL/kg Z. multiflora essential oil was mucosal NO content. NO is well-known for its role in regulating gastric blood flow which helps in maintenance of gastric mucosal integrity and can be a protective agent in ethanol-induced gastric injury (22). NO is produced by nitric oxide synthase (NOS) enzymes with constitutive and inducible expressions. NO produced by gastric endothelial NOS (eNOS) that has constitutive expression is a pivotal mediator in protection of gastric mucosa while NO produced by inducible NOS (iNOS) can participate in ulcer formation through the production of peroxide free radicals (23). In 2005, Pan et al showed that in mice with ethanol-induced gastric ulcer, 1 hour after ulcer induction the expression of eNOS and production of NO in gastric mucosa is high, where expression of iNOS increases at 3 and 6 hours after ulcer induction. In the present study sampling of gastric tissue for determination of NO content was 1 hour after ulcer induction therefore the increased level of NO due to *Z. multiflora* essential oil is possibly related to eNOS. Consistent with our study, increased NO content of stomachs with gastric ulcers induced by different methods in laboratory animals as a mechanism of gastro-protection by herbs has previously been reported. For instance, berberine (24) and *Onosma armeniacum* root extract (25) in ethanol-induced gastric injury as well as *Cordia myxa* fruit in indomethacin-induced ulcer (26) have shown NO production enhancement.

Proinflammatory cytokines such as TNF-α, IL-6 and IL-10 are important in acute phase inflammation as well as in maintenance and regulation of the severity of gastric ulcers (27) and TNF-α is involved in gastric mucosal apoptosis (28). On the contrary PGE2 enhances gastric protective mechanisms and is considered as a major gastric mucosal defensive factor (29).

Du et al reported a significant increase in TNF-α concentration of gastric mucosa of rats with ethanol-induced gastric ulcer after 1 hour which showed a reduction in rats treated with *Veronicastrum axillare* (30). El-Maraghy et al observed increased levels of TNF-α and decreased PGE2 levels in gastric tissue of rats 3 hour after ethanol administration and crocin significantly improved these changes (31). Also in a study by Li et al, 4 hours after ethanol administration in mice, TNF-α level in gastric tissue and serum was significantly increased which was attenuated with chelerythrine alkaloid (32). Moreover, in a study by AlRashdi et al, induction of gastric ulcer in rats with HCl/ethanol resulted in decreased PGE2 level in gastric mu-

cosa 1 hour after ulcer induction which was ameliorated by pretreatment with *Jasminum sambac* extract (14).

As stated in previous section of this text, we did not observe a significant difference in TNF-α and PGE2 levels among groups. The reason behind this discrepancy may be that we evaluated serum samples not gastric tissue for TNF-α. Moreover, blood collection was made only 1 hour after ulcer induction which is in contrast to the study performed by Li et al (32). Therefore, maybe more time was needed to observe a significant change in serum TNF-α level. A difference in induction method of gastric ulcer (150mM HCl/absolute ethanol in the study by Alrashdi et al, versus 75% ethanol in our study) may describe the inconsistency in PGE2 levels.

Conclusion

Z. multiflora essential oil has a gastro protective effect against ethanol-induced gastric ulcer in rats which is due to its antioxidant and NO production enhancing effect.

Authors' contributions

TS and MR had a role in hypothesis making, designing the study, data analysis and preparation of the manuscript. MR and NER contributed to data acquisition. All read and confirmed the manuscript

Conflict of interests

Authors declare no conflict of interests.

Ethical considerations

Procedures used in the present study are in accordance with institutional ethical guidelines for use of animals in experiments which are compatible with European convention for the protection of vertebrate animals used for experimental and other scientific purposes.

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