RESEARCH ARTICLE

Study of Antiulcerogenic Effect of Leaves Extract of *Origanum Vulgare* L.

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ABSTRACT

The *origanum vulgare L.* plants lamiaceae family drugs consist of abundant amount of Flavonoids, Phenolic compounds and other vital constituents responsible for curative action against peptic ulcer and also possess an antioxidant activity, In the present study one such indigenous medicinal plant *Origanum Vulgare* L. used for the treatment of ulcer in the traditional system of medicine was selected for preliminary phytochemical screening and evaluation of antiulcer activity using experimental models. Ulceration in reserpine-induced gastric ulcer model in which the animal treated with dose given as per *in vivo* model, produced significant decrease in ulcer index by 0.724 ± 0.191 ($p<0.01$) and 0.537 ± 0.153 compared with diseased control. ($p<0.001$) respectively. The extract at the dose of 200 mg/kg body weight afforded 26.33 % for EEOV. The 49.30% and 53.37 % ulcer protection for EEOVF1 and EEOVF2 respectively and whereas Omeprazole (20 mg/kg) exhibited 69.10 % ulcer protection. For anti-ulcer activity against serotonin-induced gastric ulceration in rats in which the animal treated with dose given as per *in vivo* model, produced significant decrease in ulcer index by 5.01 ± 0.31 ($p<0.01$). The extract at the dose of 200 mg/kg body weight afforded 18.16 % for EEOV. The 34.89 and 49.03 % ulcer protection for EEOVF1 and EEOVF2 respectively and whereas Omeprazole (20 mg/kg) exhibited 72.22% ulcer protection and for anti-ulcer activity against diethyldithiocarbamate-induced gastric ulceration in rats. They significantly reduced the incidence and severity of ulceration in diethyldithiocarbamate-induced gastric ulcer model. The animal treated with dose given as per *in vivo* model, produced significant decrease in ulcer index by 4.50 ± 0.53 ($p<0.01$).

Keywords: *origanum vulgare L.*, Reserpine-induced gastric ulcer model, Serotonin-induced gastric ulceration, Diethyldithiocarbamate-induced gastric ulceration, Anti-ulcer.

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INTRODUCTION

The term peptic ulcer describes a condition in which there is a discontinuity in the entire thickness of the gastric or duodenal mucosa that persists as a result of acid and pepsin in the gastric juice, Peptic ulcer disease presents to the clinicians as dyspepsia. The *origanum vulgare L.* plants lamiaceae family drugs consist of abundant amount of Flavonoids, Phenolic compounds and other vital constituents responsible for curative action against peptic ulcer and also possess an antioxidant activity,[1] antimicrobial activity, wound healing activity, analgesic activity therefore the present study aimed to overcome the problems of conventional dosage form as well as adverse effect of synthetic drugs by using herbal medicinal plant for the treatment of ulcer and provide safe, cost effective and efficacious management options as well as reduce the burden of disease. With limitation of conventional dosage form some synthetic drugs such as NSAIDS, antibiotics[2] etc. produce ulcer in stomach, to overcome such adverse effect of synthetic drugs increase the need of herbal medicinal plant to reduce such type of adverse effect. Gastric ulcers (GUs) are common pathologies that affect many people around the world. Excessive alcohol consumption is one of the main causes of GUs; however, there is still lack of effective drugs for the prevention or therapy of GUs. In this study, we evaluated the protective effects against acute ethanol-induced lesions to the gastric mucosa in mice[3]

Because of various side effects associated with synthetic antiulcer agents, the world is turning towards plant based medicaments because of their easy availability, safety and no adverse effects. Many indigenous plants have been used since ancient time for the treatment of ulcers. The *Origanum Vulgare* L. reported to have Antioxidant, Anti-inflammatory, Anti-ulcer, Wound healing, Antibacterial, Antifungal, Antimicrobial, Analgesic activity. Traditionally the plant is being used in the treatment of febrifuge and rheumatism, wounds, toothache, gonorrhea and as food for animals as well as humans. It was also reported that, the plant parts exhibits cytotoxic activity[4], radical scavenging potential, anti-motility, membrane sensitizing activity, immunomodulatory, hypoglycemic effect, anti-diarrheal, hypolipidemic and anti-fertility/spermatogenesis effect. In the present study one such indigenous medicinal plant *Origanum Vulgare* L. used for the treatment of ulcer in the traditional system of medicine was selected for preliminary phytochemical screening and evaluation of antiulcer activity using experimental models. Till date no scientific proof is available on the antiulcer activity of *Origanum Vulgare* L.

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Table 1: Physical parameters of *Origanum vulgare* L. powder

Studied parameters	Value obtained on dry weight basis (% w/w)*	Value described in API (% w/w)
Moisture content (Loss on drying)	6.02± 0.05	-----
Total ash value	10.13 ± 0.06	NMT 12 per cent
Acid insoluble ash value	0.51 ± 0.08	NMT 1 per cent
Water soluble ash value	6.02 ± 0.04	NMT 10 per cent
Alcohol extractive value	9.74 ± 0.06	NLT 9 per cent
Water extractive value	19.14 ± 0.12	NLT 15 per cent

*n=3 (Results are expressed as mean ±SEM)

Table 2: Pharmacognostic Study of *Origanum vulgare* L.

Sr. No.	Plant	Extracts	Abbreviation	Appearance	Consistency	Yield % (w/w)
1.	*Origanum*	Pet Ether	PEEOV	Greenish Yellow	Semisolid	2.0 %
2.	*vulgare L.*	Chloroform	CEOV	Pale Yellow	Semisolid	2.6 %
3.		Ethanol	EEOV	Dark Green	Semisolid	3.2 %
4.		Aqueous	AEOV	Dark Brown	Solid (Fine Powder)	4.9 %

PEE-Petroleum Ether Extract, CE-Chloroform Extract, EE- Ethanol Extract, AE-Aqueous extract, OV-*Origanum vulgare L*

Table 3: Phytochemical presents in extract of *Origanum vulgare* L.

Test for	PEEOV	CEOV	EEOV	AEOV
Alkaloids	+	+	+	+
Carbohydrates	-	-	+	+
Glycosides	-	+	-	-
Phenols and tannins	+	+	+	+
Steroids	-	-	-	-
Terpenoids	-	-	+	-
Resin	-	-	-	-
Flavonoid	-	-	+	+
Protein	-	-	+	-
Saponin	-	-	+	+

(+) = present, (-) = absent

from the reliable sources.[5,6]

MATERIALS AND METHODS

Collection and Identification

The *origanum vulgare L.* were identified and authenticated by Dr. K B Sukla Botanist Shrinathji Agriculture college Rajsamand (Raj.). The voucher specimens were deposited at the respective Institutes. *Origanum vulgare L.* voucher specimen sample number is OV-1.

Analytical Parameter

Procedure given in Indian Pharmacopoeia was used to determine the different ash values such as total ash, acid insoluble ash, and water soluble ash.[7]

Extractive Values

Extractive values of crude drugs are useful for their evaluation, especially when the constituents of a drug cannot be readily estimated by any other means. Further, these values indicate the nature of the constituents present in a crude drug Determination of Alcohol Soluble Extractive Value, Determination of Water Soluble Extractive Value as per standard procedure.[8-10]

Preparation of Extracts by Hot Extraction Method

The leaves powder of *Origanum vulgare L.* of plants were pounded and the powdered material (250 g) was extricated independently with petroleum ether, chloroform, ethanol (90%) and water utilizing hot extraction strategy. In the wake of expelling the biomass deposits by filtration, pooled removes were focused on rotating vacuum evaporator. The concentrates were additionally dried utilizing stove at 80°C with the exception of water remove. The water extricate was dried utilizing shower dryer (at delta temperature: 168 ± 2°C, outlet temperature: 107 ± 3°C, blow Speed: 12 units and air Pressure: 0.6 kg/cm^2). At last totally dried concentrates were gauged and yields were determined.[11]

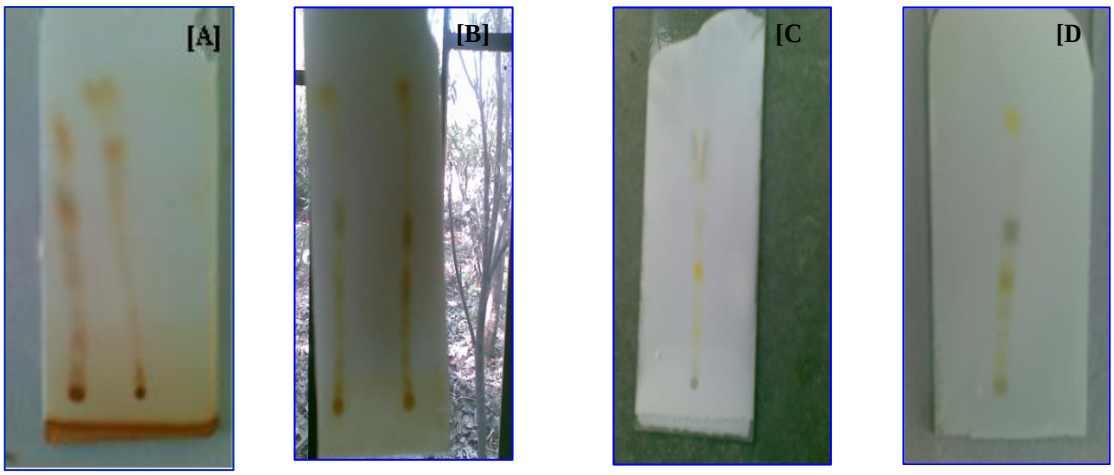


Figure 1: TLC studies of extract PEEOV [A], CEOV [B], EEOV [C], and AEOV [D] for *Origanum vulgare* L.

Table 4: TLC Studies of PEEOV, CEOV, EEOV, AEOV extract of *Origanum vulgare* L.

Fraction/ Extract	Solvent system	No of spots	TLC profile	
			R_f value	Color
PEEOV extract	Toluene:Ethylacetate:Methenol:Water (7:6:5:2)	3	0.94; 0.90; 0.74	Dark green, green, light yellow, light green
CEOV extract	Ethyl acetate: methanol: toluene: water (5:4:6:5)	6	0.82; 0.57; 0.60; 0.68; 0.71; 0.76	Dark green, light yellow light green, yellow, yellow, Cream
EEOV extract	Ethyl acetate: methanol: toluene: water (5:4:6:5)	4	0.50; 0.59; 0.62; 0.80	light yellow light green, yellow, yellow
EEOV extract	Ethyl acetate: methanol: toluene: water (5:4:6:5)	4	0.48; 0.51 0.75; 0.84	Yellow, Cream light green, yellow

Table 5: Percentage of phytoconstituents present in *Origanum vulgare* L.

Constituents presents	Quantity of phytoconstituents in (%)			
	PEEOV	CEOV	EEOV	AEOV
Alkaloids	7.12	6.23	5.14	4.43
Phenols	6.25	7.21	7.87	8.2
Tannins	4.51	4.78	5.01	5.31
Flavonoid	6.71	6.03	-	-

Qualitative Examination of Phytoconstituents

The test performed for the conformation of alkaloid, carbohydrates, glycosides, tannins and phenolics compounds, steroids, flavonoid, triterpenoids and saponins as per standard procedure[12,13]

Quantitative Determination of the Chemical Constituents

The total content of phenols in the crude all extract was determined using a modified Folin-Ciocalteu colorimetric method with Gallic acid as a standard. total alkaloid determination, total tannin determination, total flavonoid determination.[14]

Collection of Eluting Sample

It was tried to purify the compounds, which were obtained by employing column chromatography (CC) and by re-crystallizing them in different solvents. The compounds were weighed and there melting point and solubility was determined. Elute was collected at the rate of 20 drops per minute and each fraction were of about 100 ml. Each

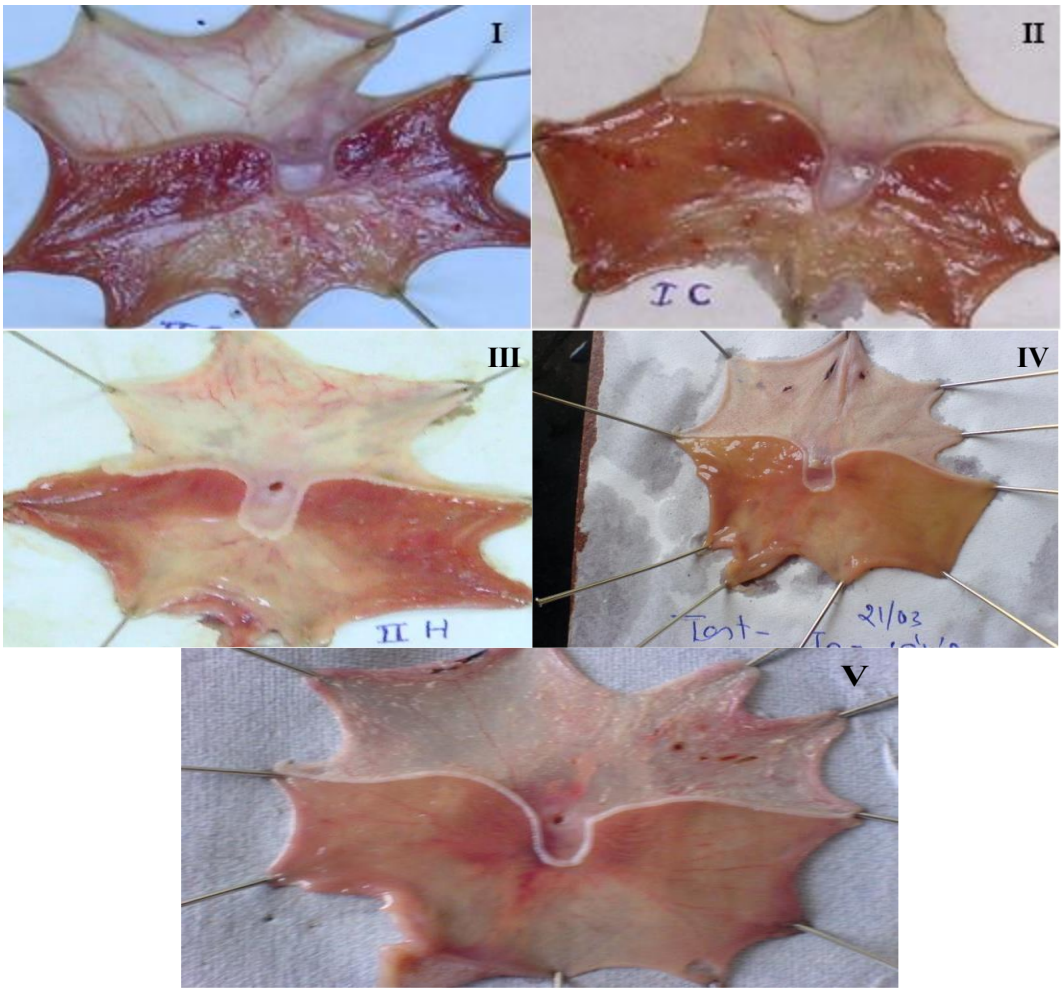


Figure 2: Photographs of reserpine-induced ulcer of rat's stomach

Table 6: Effect of EEOV and EEOVF1, EEOVF2 of leaves on reserpine-induced gastric ulceration in rats

Group	Treatment	Ulcerated area Mean ± SEM (mm2)	Ulcer index	% Protection
I	Normal saline	106 ± 6.5	1.162 ± 0.517	-
II	EEOV 200 mg/kg b.w.	93.50 ± 5.5	0.856 ± 0.274	26.33
III	EEOVF1 (20 mg/kg body weight	50.11 ± 4.0	0.750 ±0.153***	49.30
IV	EEOVF2 (20 mg/kg body weight	48.74 ± 4.0	0.537 ±0.153***	53.37
V	Omeprazole 20 mg/kg b.w. (Standard)	33.40 ± 3.3	0.359 ±0.101***	69.10

Table 7: Effect of EEOV and EEOVF1, EEOVF2 of leaves on serotonin-induced gastric ulceration in rats

Group	Treatment	Ulcer index	% Protection
I	Normal saline	9.78 ± 1.2	-
II	EEOV 200 mg/kg b.w	8.0 ± 0.91	18.61
III	EEOVF1 (20 mg/kg body weight)+ 0.5 ml serotonin creatinine sulfate	6.4 ± 0.63	34.89
IV	EEOVF2 (20 mg/kg body weight)+ 0.5 ml serotonin creatinine sulfate	5.01 ± 0.31***	49.03
V	Omeprazole 20 mg/kg b.w. (Standard)	2.73 ± 0.20***	72.22

Table 8: Effect of EEOV and EEOVF1, EEOVF2 of leaves on Diethyldithiocarbamate-induced gastric ulcer in rats

Group	Treatment	Ulcer index	% Protection
I	Normal saline + (800mg/kg sc body weight)	6.45 .± 0.7	-
II	EEOV 200 mg/kg b.w	6.2 ± 0.12	20.16
III	EEOVF1 (20 mg/kg body weight)+ 1mL diethyldithiocarbamate in saline	4.32 ± 0.02	48.22
IV	EEOVF2 (20 mg/kg body weight)+ 1mL diethyldithiocarbamate in saline	4.50 ± 0.53***	38.90
V	Omeprazole 20 mg/kg b.w. (Standard)	3.00 ± 0.65***	53.5

(Mean ±SEM; N=6 in each group) ** p<0.01, ***p<0.001 (VS Diseased control)

fraction were subjected to TLC on silica gel G.[15] The fractions with same R_f were pooled together and concentrated to obtain pure compounds or a mixture of 2-3 compounds. The Ethanolic soluble fraction obtained from ethanolic extract of *Origanum vulgare L.* was packed in a column. The elution in the silica gel column was started with hexane and thereafter ethyl acetate was added up to 100% and then methanol was gradually added from 10- 100 %. The fractions (100 ml) were collected from the column and those having the same TLC profile were mixed together.[16] The mixed crude fractions from the column were subjected to re chromatography in silica gel column.

Spectral Analysis and Structural Elucidation

The identification of a molecule was done through the interpretation of the data obtained from spectroscopic analysis. Tools for vital structure elucidation of natural products are Fourier transform infrared spectroscopy (FTIR) Agilent Cary 630 FTIR spectrometer , mass spectrometer (MS) Agilent 6520 (Q-TOF) , and nuclear magnetic resonance spectroscopy (NMR) Bruker II Avance 400 FT-NMR . With these tools the structures of most natural products can be determined.

Evaluation of Anti-ulcer Activity

Experimental Peptic Ulcer Models Peptic ulcers can be induced by physiological, pharmacological or surgical manipulations in several animal species. However, most experiments in peptic ulcer studies are carried out in rodents. Several models are used experimentally for testing or evaluating antipeptic ulcer activity of drugs/agents, and these include the following: reserpine-induced gastric ulcers; serotonin-induced gastric ulcers; diethyldithiocarbamate- (DDC)-induced peptic ulcers; ferrous iron-ascorbic acid induced gastric ulcers.[17]

Reserpine-induced Peptic Ulcer

Scientists have also used reserpine to induce ulcers. Reserpine-induced gastric ulcera tion has been attributed to the degranulation of gastric mast cells consequent to liberation of histamine, believed to be mediated by the cholinergic system. Rats fasted for 36 hours are administered reserpine dissolved in 10% Tween 80 (5–8mg/kg, i.p.) in. Although the model is acid dependent, hypermotility seems to be more important than hypersecretion for the induction of gastric mucosal lesion. Normally, drugs or plant extracts to be evaluated Ulcers are administered to the test animals, at least, 30 minutes before the administration of the reserpine. The test animals are then sacrificed 24 hours later.[18]

I Received normal saline + 1 ml reserpine dissolved in 10% Tween 80 (5 mg/kg, i.p diseased control).

II Received E E O V / E E N N (200 mg/kg bodyweight) + 1 ml reserpine dissolved in 10% Tween 80 (5 mg/kg, i.p diseased control), (Average Medium dose).

III Received EEOVF1/EENNF1 (20 mg/kg bodyweight) + 1 ml of diseased control

IV Received EEOVF2/EENNF2 (20 mg/kg bodyweight) + 1 ml of diseased control

V Received reference drug, Omeprazole (20 mg/kg body weight) + 1 ml of diseased control

Serotonin-induced Gastric Ulcer

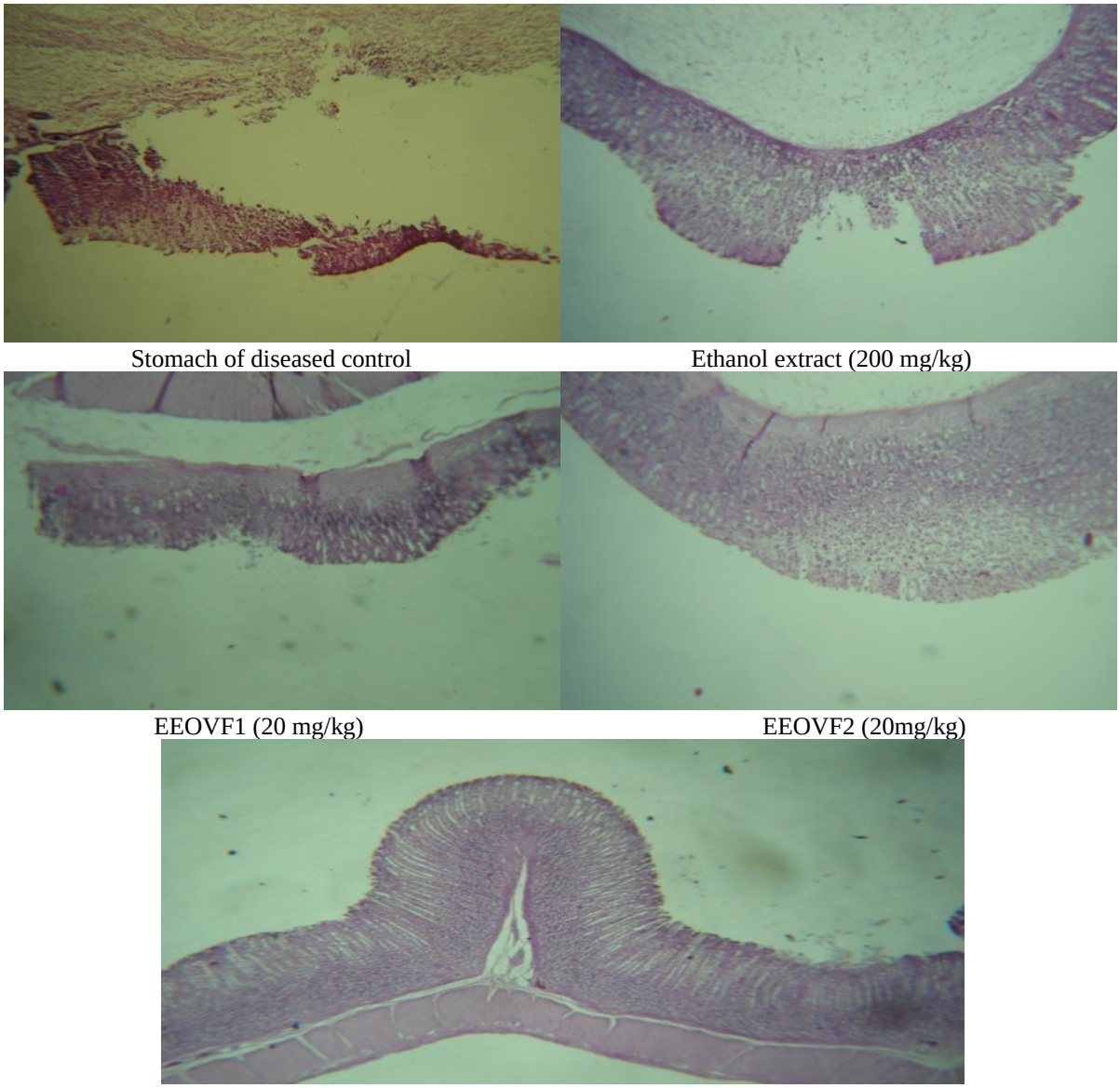
Serotonin, which has also been used to induce ulcers, is known to cause vaso constriction, thereby reducing gastric mucosal blood flow (GMBF) result in ginacute mucosal injury. In this model, rats are fasted for 24–36 hours. The fasted animals are denied of water 2 hours just before commencement of the experiments. Glandular lesions are established following the administration of a single dose of serotonin creatinine sulfate (0.5 mL of 50mg/kg subcutaneous injection). Serotonin is administered by in tragastric intubation with the aid of an orogastric cannula.[19] The animals are sacrificed by cervical dislocation 6 hours later.

I Received normal saline + 0.5 ml serotonin creatinine sulfate (0.5 mL of 50mg/kg subcutaneous injection). (Diseased control).
II Received E E O V / E E N N (200 mg/kg bodyweight) (Average Medium dose) + 0.5 ml serotonin creatinine sulfate (50 mg/kg, sc diseased control).
III Received EEOVF1/EENNF1 (20 mg/kg bodyweight) + 0.5 ml of diseased control
IV Received EEOVF2/EENNF2 (20 mg/kg bodyweight) + 0.5 ml of diseased control
V Received reference drug, Omeprazole (20 mg/kg body weight) + 0.5 ml of diseased control

Diethyldithiocarbamate-induced Gastric Ulcer

The diethyldithiocarbamate model is used to assess the antioxidant activities of drugs in the prevention of gastric damage. This model is also used to assess the cytoprotective actions of potential drugs. diethyldithiocarbamate has been reported to induce antral lesions through the mobilization of superoxide and hydroxyl radicals. Superoxide radical and hydroxyl radicals play a pathogenic role in the induction of this ulcer. Acute glandular lesions are induced by subcutaneous administration of of 1mL diethyldithiocarbamate in saline (800mg/kg body weight) followed by 1Ml oral dose of 0.1NHCl. In this model, food is also withdrawn 24 hours and water 2 hours just before the commencement of the experiment.[20]

I Received normal saline + 1mL diethyldithiocarbamate in saline (800mg/kg sc body weight) (Diseased control).



Stomach of diseased control | Ethanol extract (200 mg/kg)

EEOVF1 (20 mg/kg) | EEOVF2 (20mg/kg)

Omeprazole (20 mg/kg, p.o.)

Figure 3: Histopathology of rat's stomach induced by reserpine

II Received E E O V / E E N N (200 mg/kg bodyweight) (Average Medium dose) + 1mL diethyldithiocarbamate in saline (800mg/kg sc body weight) (Diseased control).
III Received EEOVF1/EENNF1 (20 mg/kg bodyweight) + 1 ml of diseased control
IV Received EEOVF2/EENNF2 (20 mg/kg bodyweight) + 1 ml of diseased control
V Received reference drug, Omeprazole (20 mg/kg body weight) + 1 ml of diseased control

RESULTS AND DISCUSSION

Physical Parameters of *Origanum Vulgare* L.

Preliminary Phytochemical Analysis of *Origanum Vulgare* L.

Phytochemical screening of the ethanol concentrate and water concentrate of *Origanum vulgare L.* leaf powder indicated the nearness of different phytoconstituents.

UV spectra have shown maximum absorption due to substitution of functional group in compound. The IR spectrum of compounds (EEOVF1) showed absorption bands characteristics of flavanol indicating the presence of hydroxyl and tinsoporin functionalities at 3449, 1375 and 1079 cm^{-1} respectively, indication of double bond were represented by 1689 cm^{-1}. peak at 1375 cm^{-1} represented C-H bending where as NMR spectra was also characteristic of phytotaxanol, exhibiting the hydroxyl proton signal at δ 5.21as a multiplet, which helped us to characterize this compound as taxaterone, tinsoporin.

Anti-ulcer Activity

Reserpine-induced Peptic Ulcer

The EEOV, EEOVF1, EEOVF2 were evaluated for its anti-ulcer activity against reserpine-induced gastric ulceration in rats. The results are tabulated (Table No.6). They significantly reduced the incidence and severity of ulceration in reserpine-induced gastric ulcer model. The animal treated with dose given as per in vivo model, produced significant decrease in ulcer index by 0.724 ± 0.191 ($p<0.01$) and 0.537 ± 0.153 compared with diseased control. ($p<0.001$) respectively. The extract at the dose of 200 mg/kg body weight afforded 26.33 % for EEOV. The 49.30 and 53.37 % ulcer protection for EEOVF1 and EEOVF2 respectively, whereas Omeprazole (20 mg/kg) exhibited 69.10 % ulcer protection.

Serotonin-induced Gastric Ulcer

The EEOV, EEOVF1, EEOVF2 were evaluated for its anti-ulcer activity against serotonin-induced gastric ulceration in rats. The results are tabulated (Table No.7). They significantly reduced the incidence and severity of ulceration in serotonin-induced gastric ulcer model. The animal treated with dose given as per *in vivo* model, produced significant decrease in ulcer index by 5.01 ± 0.31 ($p<0.01$). The extract at the dose of 200 mg/kg body weight afforded 18.16 % for EEOV. The 34.89 and 49.03 % ulcer protection for EEOVF1 and EEOVF2 respectively whereas Omeprazole (20 mg/kg) exhibited 72.22% ulcer protection

Diethyldithiocarbamate-induced Gastric Ulcer

The EEOV, EEOVF1, EEOVF2 were evaluated for its anti-ulcer activity against diethyldithiocarbamate-induced gastric ulceration in rats. The results are tabulated (Table No.8). They significantly reduced the incidence and severity of ulceration in diethyldithiocarbamate-induced gastric ulcer model. The animal treated with dose given as per in vivo model, produced significant decrease in ulcer index by 4.50 ± 0.53 ($p<0.01$). The extract at the dose of 200 mg/kg body weight afforded 20.16 % for EEOV. The 48.22 and 38.90 % ulcer protection for EEOVF1 and EEOVF2 respectively whereas Omeprazole (20 mg/kg) exhibited 53.50 % ulcer protection respectively.The results were expressed as Mean ± S.E.M. and statistical significance by means of One-way ANOVA followed by Tukey-Kramer multiple comparisons test.

CONCLUSION

The extract and fraction of (EEOV, EEOVF1, EEOVF2) Origanum Vulgare L. were evaluated for its anti-ulcer activity against reserpine-induced gastric ulceration in rats. They significantly reduced the incidence and severity of ulceration in reserpine-induced gastric ulcer model. The animal treated with dose given as per in vivo model, produced significant decrease in ulcer index by 0.724 ± 0.191 ($p<0.01$) and 0.537 ± 0.153 compared with diseased control. ($p<0.001$) respectively. They significantly reduced the incidence and severity of ulceration in serotonin-induced gastric ulcer model. The animal treated with dose given as per in vivo model, produced significant decrease in ulcer index by 5.01 ± 0.31 ($p<0.01$). The extract at the dose of 200 mg/kg body weight afforded 18.16 % for EEOV. The 34.89 and 49.03 % ulcer protection for EEOVF1 and EEOVF2 respectively whereas Omeprazole (20 mg/kg) exhibited 72.22% ulcer protection for anti-ulcer activity against diethyldithiocarbamate-induced gastric ulceration in rats. For anti-ulcer activity against serotonin-induced gastric ulceration in rats. They significantly reduced the incidence and severity of ulceration in reserpine-induced gastric ulcer model. The animal treated with dose given as per in vivo model, produced significant decrease in ulcer index by 5.01 ± 0.31 ($p<0.01$). They significantly reduced the incidence and severity of ulceration in diethyldithiocarbamate-induced gastric ulcer model. The given above animal model were used for investigate the anti-ulcer activity of extract and their isolated compounds, the study summarized that plant extract give significant anti-ulcer activity as the compared with standard drug.

Abbreviation: OV- *Origanum Vulgare* L. EEOV- ethanolic extract of *Origanum Vulgare* L., EEOVF1-first fraction of ethanolic extract of *Origanum Vulgare* L., EEOVF2 second fraction of ethanolic extract of *Origanum Vulgare* L.,

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