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Pharmacology

"GASTROPROTECTIVE ACTIVITY OF TRACHYSPERMUM AMMI AGAINST ETHANOL INDUCED GASTRIC ULCERS"

Dr. B. Raghuveer Associate Professor, Department of Pharmacology, KIMS-Narketpally, Nalgonda-508254, Telangana-India. - Corresponding Author:

Dr. K. Chakravarthy Associate Professor, Department of Pharmacology, SVS medical college, Yenukonda, Mahboobnagar-509001-Telangana-India.

ABSTRACT About 4 million people have active peptic ulcers and about 350,000 new cases In the United States are diagnosed each year. Four times as many duodenal ulcers as gastric ulcers are diagnosed. Approximately 3,000 deaths per year in the United States are due to duodenal ulcer and 3,000 to gastric ulcer. The lifetime risk for developing a peptic ulcer is approximately 10%. In Western countries the prevalence of *Helicobacter pylori* infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80 etc.). Prevalence is higher in third world countries. Transmission is by food, contaminated. A minority of cases of *H. pylori* infection groundwater, and through human saliva (such as from kissing or sharing food utensils) will eventually lead to an ulcer and a larger proportion of people will get non-specific discomfort, abdominal pain or gastritis. Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century, when epidemiological trends started to point to an impressive fall in its incidence. The reason that the rates of peptic ulcer disease decreased is thought to be the development of new effective medication and acid suppressants and the discovery of the cause of the condition, *H. pylori.*

KEYWORDS : ethanol, gastric ulcers, gastro-protective activity, ajwain, GIT.

INTRODUCTON[1-21]

The stomach is a muscular, hollow, dilated part of the digestion system which functions as an important organ of the digestive tract in some animals, including vertebrates, echinoderms, insects (mid-gut), and molluscs. It is involved in the second phase of digestion, following mastication (chewing). The stomach is located between the esophagus and the small intestine. It secretes protein-digesting enzymes and strong acids to aid in food digestion, (sent to it via oesophageal peristalsis) through smooth muscular contortions (called segm entation) before sending partially digested food (chyme) to the small intestines. The word *stomach* is derived from the Latin *stomachus* which is derived from the Greek word *stomachos,* ultimately from *stoma,* "mouth". The words *gastro-* and gastric (meaning related to the stomach) are both derived from the Greek word *gaster*

Role in digestion:

Bolus (masticated food) enters the stomach through the oesophagus via the oesophageal sphincter. The stomach releases proteases (protein-digesting enzymes such as pepsin) and hydrochloric acid, which kills or inhibits bacteria and provides the acidic pH of two for the proteases to work. Food is churned by the stomach through muscular contractions of the wall called peristalsis – reducing the volume of the fundus,[3] before looping around the fundus and the body of stomach as the boluses are converted into chyme (partially digested food). Chyme slowly passes through the pyloric sphincter and into the duodenum, where the extraction of nutrients begins. Depending on the quantity and contents of the meal, the stomach will digest the food into chyme anywhere between forty minutes and a few hours.

Table No. 1: The stomach is divided into four sections, each of which has different cells and functions. The sections are:

Cardia	Where the contents of the oesophagus empty into the stomach.
Fundus	Formed by the upper curvature of the organ.
Body or Corpus	The main, central region.
Pylorus	The lower section of the organ that facilitates emptying the contents into the small intestine.

Fig No.1 Sections of the stomach

Blood supply

.Fig No. 2 Schematic image of the blood supply to the stomach: left and right gastric artery, left and right gastro-omental artery and short gastric artery

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Fig No.3 Celiac artery and its branches.

A more realistic image, showing the celiac artery and its branches; the liver has been raised, and the lesser omentum and anterior layer of the greater omentum removed. The lesser curvature of the stomach is supplied by the right gastric artery inferiorly, and the left gastric artery superiorly, which also supplies the cardiac region. The greater curvature is supplied by the right gastro-epiploic artery inferiorly and the left gastro-epiploic artery superiorly. The fundus of the stomach, and also the upper portion of the greater curvature, is supplied by the short gastric artery which arises from splenic artery. Like the other parts of the gastrointestinal tract, the stomach walls are made of the following layers, from inside to outside:

Classification

1) Duodenum (called duodenal ulcer)
2) Oesophagus (called esophageal ulcer)
3) Stomach (called gastric ulcer)
4) Meckel's diverticulum (called Meckel's diverticulum ulcer; is very tender with palpation)

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Fig No. 4 Deep Gastric Ulcer

Modified Johnson Classification of peptic ulcers:

Type **I:** Ulcer along the body of the stomach, most often along the lesser curve at incisura angularis along the locus minoris resistantiae.
Type **II:** Ulcer in the body in combination with duodenal ulcers. Associated with acid oversecretion.
Type **III:** In the pyloric channel within 3 cm of pylorus. Associated with acid oversecretion.
Type **IV:** Proximal gastroesophageal ulcer
Type **V:** Can occur throughout the stomach. Associated with chronic NSAID use (such as aspirin).

Signs and symptoms

Symptoms of a peptic ulcer can be

1) Abdominal pain, classically epigastric with severity relating to mealtimes, after around three hours of taking a meal (duodenal ulcers are classically relieved by food, while gastric ulcers are exacerbated by it);
2) bloating and abdominal fullness;
3) Water brash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus - although this is more associated withgastroesophageal reflux disease);
4) Nausea, and copious vomiting;
5) Loss of appetite and weight loss;
6) hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer, or from damage to the esophagus from severe.continuing vomiting.
7) Melena (tarry, foul-smelling feces due to oxidized iron from

hemoglobin);

8) Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis. This is extremely painful and requires immediate surgery.

A history of heartburn, gastroesophageal reflux disease (GERD) and use of certain forms of medication can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAID (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase, and most glucocorticoids (e.g. dexamethasone and prednisolone).

In patients over 45 with more than two weeks of the above symptoms, peptic ulcer is only found in pre-teen and young adults, rarely will you find peptic ulcer in a adult, the odds for peptic ulceration are high enough to warrant rapid investigation by esophago-gastro-duodenoscopy.

The timing of the symptoms in relation to the meal may differentiate between gastric and duodenal ulcers: A gastric ulcer would give epigastric pain during the meal, as gastric acid production is increased as food enters the stomach. Symptoms of duodenal ulcers would initially be relieved by a meal, as the pyloric sphincter closes to concentrate the stomach contents; therefore acid is not reaching the duodenum. Duodenal ulcer pain would manifest mostly 2–3 hours after the meal, when the stomach begins to release digested food and acid into the duodenum.

Also, the symptoms of peptic ulcers may vary with the location of the ulcer and the patient's age. Furthermore, typical ulcers tend to heal and recur and as a result the pain may occur for few days and weeks and then wane or disappear. Usually, children and the elderly do not develop any symptoms unless complications have arisen.

Burning or gnawing feeling in the stomach area lasting between 30 minutes and 3 hours commonly accompanies ulcers. This pain can be misinterpreted as hunger, indigestion or heartburn. Pain is usually caused by the ulcer but it may be aggravated by the stomach acid when it comes into contact with the ulcerated area. The pain caused by peptic ulcers can be felt anywhere from the navel up to the sternum, it may last from few minutes to several hours and it may be worse when the stomach is empty. Also, sometimes the pain may flare at night and it can commonly be temporarily relieved by eating foods that buffer stomach acid or by taking anti-acid medication.However, peptic ulcer disease symptoms may be different for every sufferer.

CAUSES:

A major causative factor (60% of gastric and up to 90% of duodenal ulcers) is chronic inflammation due to *Helicobacter pylori* that colonizes the antral mucosa The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis) resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion can either be increased, or as in most cases, decreased, resulting in hypochlorhydria. Gastrin stimulates the production of gastric acid by parietal cells. In *H. pylori* colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation.

Another major cause is the use of NSAIDs . The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (*cox-1*), which is essential for the production of these prostaglandins COX-2 selective anti-inflamm atories (such as celecoxib or the since withdrawn rofecoxib) preferentially inhibit *cox-2,* which is less essential in the gastric mucosa, and roughly halve the risk of NSAID-related gastric ulceration.

The incidence of duodenal ulcers has dropped significantly during the last 30 years, while the incidence of gastric ulcers has shown a small increase, mainly caused by the widespread use of NSAIDs. The drop in incidence is considered to be a cohort-phenomenon independent of the progress in treatment of the disease. The cohort-phenomenon is probably explained by improved standards of living which has lowered the incidence of *H. pylori* infections.

Although some studies have found correlations between smoking and ulcer formation, others have been more specific in exploring the risks involved and have found that smoking by itself may not be much of a risk factor unless associated with *H. pyloriinfection.* Some suggested risk factors such as diet, and spice consumption, were hypothesized as ulcerogens (helping cause ulcers) until late in the 20th century, but have been shown to be of relatively minor importance in the development of peptic ulcers.

TYPES OF AGENTS INDUCING ULCERS:

1) Ethanol induced gastric ulcers
2) Acetic acid induced gastric ulcers
3) Indomethacin induced gastric ulcers
4) Pylorus ligation induced gastric ulcers
5) Corticosteroids induced ulcers
6) Cysteamine induced duodenal ulcers

STANDARD DRUG:

Ranitidine A Non-Imidazole (has a furan ring) n H2 blocker, it has several desirable features compared to Cimetidine:

1) About 5 times more potent than Cimetidine. Though it's pharmacokinetic profile and t1.2 of 2-3 hr is similar to Cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency.
2) No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism-no effect on male sexual function or gynaecomastia.
3) Lesser permeability into the brain: lower propensity to cause CNS effects. In fact, little effect outside g.i.t. has been observed.
4) Does not significantly inhibit hepatic metabolism of other drugs; drug interactions mostly have no clinical relevance.
5) Overall incidence of side effects is lower: headache, diarrhoea. constipation, dizziness have an incidence similar to placebo.

Dose:

For ulcer healing 300 mg at bed time or 150 mg BD. For maintenance 150 mg at bed time. Parenteral dose-- 50 mg i.m. or slow i.v. inj every 6-8 hr (rapid i.v injection can cause hypotension), 0.1-0.25 mg.kg.hr by i.v. infusion has been used for prophylaxis of stress ulcers. For gastrinoma 300 mg 3-4 times a day. ULTAC, ZINETAC 150 mg, 300 mg tabs;

HISTAC, RANITINE, ACILOC, RANTAC 150 mg, 300 mg tab;

TRACHYSPERMUM AMMI: Ajwain seeds

AJWAIN is a native of Egypt and is cultivated in Iraq, Iran, Afghanistan, Pakistan, India

Trachyspermum ammi L.belonging to family Apiaceae a highly valued medicinally important seed spice. The roots are diuretic in nature and the seeds posses excellent aphrodisiac properties. The seeds contain brown coloured oil known as "ajwain oil".The main component is Thymol, which is used as gastrointestinal ailments,lack of appetite and bronchial problems.

FIG No. 5 Trachyspermum ammi seeds

Plant taxonomy:

1) Kingdom: Plantae
2) Subkingdom: Tracheobionta
3) Superdivision:Spermatophyta
4) Division: Magnoliophyta
5) Class: Magnoliopsid (Dicotyledons)
6) Subclass: Magnoliidae
7) Order: Apiales
8) Family: Apiacea
9) Genus:Trachyspermum
10) Species: Ammi

Common name: AJWAIN
Botanical name: Trachyspermum ammi

DESCRIPTION:

Ajwain is profusely branched annual herb, 60-90cm tall, stem is striated, inflorescence, compound umbel, with 16 umbellets, each umbellets, each containing upto 16 flowers. Flowers are actinomorphi c, white male and bisexual. Leaves are pinnate,with a terminal and 7 pairs of lateral leaflets. Fruits consists of 2 mericarps , grayish, brown, ovoid, compressed, about 2mm long, and 1.7mm wide,5 ridges and 6

vittae in each mericarp, usually saperate,5 primary ridges.

ORIGIN AND DISTRIBUTION:
It is a native of Egypt and is cultivated in Iraq, Iran, Afghanistan, Pakistan, and India.In India,it is cultivated in Madhya Pradesh, Uttar Pradesh,Gujarath, Rajasthan, Maharashtra, Bihar and West Bengal. Trachyspermum ammi L. belonging to family Apiaceae a highly valued medicinally important seed spice.

CHEMICAL CONSTITUENTS: [22-25]
Ajwain contains many phytoconstituents including carbohydrates, glycosides, saponins, phenolic compounds, volatile oil (thymol, γ-terpinene, para-cymene, and α- and β-pinene), protein, fat, fibre and mineral matter containing calcium, phosphorous, iron and nicotinic acid.

AIM AND OBJECTIVES
The aim of the present study was to investigate and compare the gastroprotective effect of different doses (250,500mg.kg of body weight (b.wt.) of ajwain extracts with antiulcer drug.

General objectives:
To investigate the Antiulcer activity of different doses of Hydroalcoholic(50% Ethanol and 50% water) extract of ***Trachyspermum ammi***

Specific objectives:
1. Phytochemical screening of trachyspermum ammi extract.
2. Acute toxicity studies by OECD 423 guidelines.
3. Screening for study of anti-ULCER activity of the seeds of Trachyspermum ammi

a) By using ethanol induced model
i. Gastric volume
ii. Acidity
iii. total acidity

MATERIALS AND METHODS [26-51]

Plant material and extract preparation:
Trachyspermum ammi was collected from the S.V. University, Tirupati, and authentified from Dr.Madhav Chetty, Department of Botany, S.V. University, Tirupati.

Plant material was dried under shadow and extraction was carried out by cold maceration.The ajwain seeds was grounded in a milling machine in order to obtain a fine dry powder. The powder was weighed, using a single pan electronic weighing balance ,and the ajwain extract was obtained by means of a maceration process. The ajwain powder was soaked in 50% ethanol and 50% distilled water (1 g of powder per 5 ml of solvent) in a 250 ml Erlenmeyer flask for a period of 4-5 days at room temperature with frequent shaking. The flasks were closed with a cotton plug and aluminium foil. The mixture was then centrifuged at 3,500 × g for 20 min and finally filtered through Whatmann filter paper No.1. The filtrate was collected and concentrated under reduced pressure in a rotary vacuum evaporator until a semi-solid substance was obtained, which was then dried in a crucible under a controlled temperature (45ºC) to obtain a solid powder . The process of extraction was repeated until 500 mg of the powder was obtained. The powder was weighed, reconstituted in dimethyl sulfoxide (DMSO) and stored at 4ºC. Once the extracts are dissolved in pure DMSO, these are also sterilized, and thus, a very costly and time-consuming step of membrane filtration sterilization was omitted.

Animals:
Forty eight albino rats, Wister strain weighing 160±10g, were obtained from Animal House. The animals were housed in well ventilated cage and animals had 12 hours day and night schedule with temperature between 20 - 28˚C. The animals were housed in large spacious hygienic cages during the course of the experimental period. The animals were allowed free access to standard laboratory pellets and drinking water ad libitum. The study protocol was approved by CPCSEA, IAEC.

Drugs and Chemicals:
Anti-ulcer agent (Zantac ™ (Ranitidine) was obtained in the form of ampoules from pharmacy., Ethanol, distilled water, chloroform, sodium hydroxide ,phentholin, topper's reagent, normal saline, dimethyl sulfoxide.

PhytoChemical Screening of Hydroalcoholic Extract of Trachys permum Ammi :
Test for carbohydrates and or.glycosides:
Five g of the air-dried powder of plant were boiled with 20 ml distilled water. The aqueous solution was filtered and the filtrate was tested for the presence of carbohydrates and glycosides using the procedures described by Harper (1975) and Balbaa (1986).

Molisch's test: Two ml of the prepared filtrate were mixed with 0.2 ml of alcoholic solution of α-naphthol 10% in addition to 2 ml of Sulphuric acid, a bluish violet zone is formed this indicates the presence of carbohydrates and .or glycosides.

Fehling's test: In a test tube 5 ml of the filtrate were treated with 5 ml Fehling's solutions (A & B) and heated; the appearance of a red precipitate indicates the presence of reducing sugars.

Benedict's test: To 1 ml of the filtrate, 5 ml of Benedict's reagent were added. The mixture was heated; appearance of red precipitate indicated the presence of reducing sugars.

Test for alkaloids and .or nitrogenous bases: About 10 g of the air-dried powder of the studied plant were extracted with 50 ml dil. hydrochloric acid. The acidic filtrate was rendered alkaline with ammonium hydroxide and extracted with three successive portions (each 15 ml of chloroform). The chloroform extracts were evaporated till dryness and the residues were dissolved in 2 ml of dilute hydrochloric acid and tested with Mayer's and modified Dragendorff's reagent (Fulton,1932).

Mayer's reagent: When added to the residue solution, turbid or white precipitate was formed; this indicates the presence of alkaloids.

Dragendorff's reagent: When added to the residue solution an orange precipitate was formed, this indicates the presence of alkaloids.

EXPERIMENTAL MODELS: [52-69]
Ethanol induced gastric ulcer in rats : ANIMALS: Albino rats. (2 animals in each group)
Group I : Control group
Group II : Ethanol(1 ml)
Group III : 250mg.kg of oral doses of hydroalcoholic extract of ajwain+Ethanol (1 ml)
Group IV : 500mg.kg of oral doses of hydroalcoholic extract of ajwain+Ethanol (1 ml)
Group V : Standard drug (Rantidine 20mg.kg) + Ethanol (1 ml)

Experimental design:
All Animals were fed on the basal diet and water ad libitum and they were maintained under healthy conditions of humidity, temperature (20-25°C) and light (12-h light: 12-h dark cycle) for one week before starting the experimental to acclimatization. After acclimatization period, rats were divided into five groups of equal weight and number (6 rats eachAnimals were randomly divided into six groups of six animals each. Group I served as control, Group II to VI were the drug treated groups. ajwain hydroalcoholic extract 100 mg.kg body weight and ranitidine 20 mg.kg body weight respectively by oral route for a period of 5 days.

On day 5, one hour after the administration of Ajwain extracts . Ranitidine all the animals received absolute ethanol (1ml.rat p.o.). One hour after administration of ethanol, the animals were sacrificed and the stomach was then excised and cut along the greater curvature, washed carefully with 5.o ml of 0.9% NaCl and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of stomach.

Macroscopic evaluation of stomach:
The stomachs were opened along the greater curvature, rinsed with saline to remove gastric contents and blood clots and examined by a×5 magnifier lens to assess the formation of ulcer. The number of ulcers was counted. Ulcer scoring was under taken according to Vogel et al. (14).The scores were: 0 = no ulcer, 1= superficial ulcer, 2= deep ulcer, 3= perforation. Ulcer area was assessed by using 3 Mscaled surgical transpore tapes, which was fixed on a light and transparent sheet. Each cell on the tape was 1mm2 in area, so the number of cells was counted

and the ulcer area was measured for each stomach Ulcer index was measured by using following formula according to Vogel et al. The stomach samples were scanned using a computer scanner and the total mucosal area and total ulcerated area was measured using public domain image processing and analysis program.

UI = UN + US + UP × 10-1
Which UI = ulcer index,
UN = mean of ulcer number,
US =mean of ulcer score,
UP = ulcer probability (incidence %) for each group.

The ulcers were given scores based on their intensity as follows: 0 ¼ no ulcer, 1 ¼ superficial mucosal erosion, 2 ¼ deep ulcer or transmural necrosis, 3 ¼ perforated or penetrated ulcer.The stomach samples from groups that showed reduction in ulcer index were subsequently processed for histological examination.

Statistical analysis

The statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Dunnet's comparison test. For comparing nonparametric ulcer scores, ANOVA followed by non-parametric Dunn posttest was used. The values are expressed as mean _ SEM, and $p < 0.05$ was considered significant.

RESULTS

Table No. 2: Phytohemical screening of Trachyspermum ammi.

S.NO	Constituents	Tests	Presence.absence
1.	Carbohydrates	Molisch`s test	+
2.	Alkaloids	Dragendroff`s test	+
3.	Amino acids	Ninhydrin test	_
4.	Volatile oil		+
5.	Flavanoids	Alkaline reagent test	+
6.	Tannins	Ferric chloride test	+
7.	Steriods and Triterpeoids	Salwoski test	+

+=positive, -=negative

Ethanol-induced gastric ulcers:

The hydroalcoholic extracts of *Trachyspermum ammi* showed a significant reduction in ulcer index when compared with control ($p < 0.05$) in Table No.3

Table- No.3:

Effect of *Trachyspermum ammi* extracts in ethanol-induced gastric ulcers compared with control and standard drug Ranitidine.

Treatment	Ethanol Ulcer index	Ulcer score
Control	0.0 ± 0.0	0.0 ± 0.0
Ethanol	5.01±0.21	10.02.046**
Ethanol + Hydroalcoholic Extract (250mg.kg)	3.43±0.024**	5.1±0.24**
Ethanol + Hydroalcoholic Extract (500mg.kg)	2.21 ± 0.028**	2.3± 0.26**
Ethanol + Ranitidine(20mg.kg)	1.09± 0.032**	1.2± 0.12**

Fig No. 6 Graph 1:

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Fig No. 7 Graph 2:

Histopathological examination of ethanol-induced gastric ulcers in rats:

The stomachs of the scarified rats were taken and immersed in 10% formalin solution. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. Specimens were then cleared in xylol, embedded in paraffin, sectioned at 4-6 microns thickness and stained with Heamtoxylin and Eosin stain for examination of the stomach as described by Carleton, (1979).

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Fig No. 8 **Group I** Fig No. 9 **Group II**

Fig No. 10 **Group 111** Fig No. 11 **Group IV**

Fig No. 12 **Group V**

Fig No. 13 **Group-I (Control):** Shows normal stomach of rats.

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Fig No. 14 **Group-II (control group+ toxicant)**

Shows Stomach of rats with congestion, hemorrhagic, necrosis, involving full thickness of mucosa with ulceration and sloughing off of upper half of mucosa in some areas. Multiple large ulcers involving complete thickness of mucosa in some areas.

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Fig No. 15 **Group-III- (250mg.kg of extract of Ajwain + toxicant)**

Shows Stomach of rats with Focal ulcerations and necrosis involving upper half of the mucosa. Single large shallow ulcer- less severity.

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Fig No. 16 **Group-4(500mg.kg of hydroalcoholic extract of ajwain+ toxicant)**

Shows Stomachs of rats with superficial erosion of mucosa – surface epithelium 2-3 small areas of erosion.

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Fig No. 17 **Group-V (standard drug+ toxicant)**

Shows Stomach of rats with Focal shallow small mucosal ulcerations

DISCUSSION

It is generally accepted that gastric ulcers results from an imbalance between aggressive factors and the maintenance of the mucosal integrity through the endogenous defense mechanism. The role of free radicals is also reported in the indication of ulcers. Prostaglandins (PG) offer protection to duodenum through both increases in mucosal resistance as well as decrease in aggressive factors, mainly acid and pepsin. Ethanol induced gastric ulcers have been widely used for the evaluation of gastro protective activity. Ethanol is metabolized in the body and releases superoxide anion and hydroxyl and peroxyl free radicals. The incidence of ethanol induced ulcers is predominant in the glandular part of stomach. It was reported stimulate the formation of leukotriene C4 (LTC4), mast cell secretory products and reactive oxygen species resulting in the damage of rat gastric mucosa. In this study, ranitidine is used as reference drug to delineate in part the mechanism(s), which are probably involved in ulcer pathogenesis. The results obtained in reference groups indicate that ajwain extract possesses its anti-ulcerative properties through a mechanism mainly related to acid and pepsin inhibition. A knowledge of the chemical composition of a given plant extract is required in order to extrapolate the proposed mechanism of actions to its possible in vivo efficacy (or safety). Hence, the healing of gastric ulcers in ethanol–induced gastric ulcers may be due to decreased acid secretion ,increased mucus secretion, or decreased GI motility incase of hydro alcoholic extracts, and the ulcer healing effect mainly due to reduction in gastric motility and its antiulcer activity may be due to the presence of these chemical constituents in the plant. Trachyspermum ammi produced antiulcer activity in all the model taken up for the study. Hydroalcoholic extract at the doses, reduces ulcer incidence significantly ($P<0.01$) when compared to the control as evident by decrease in ulcer score in the entire model. Protection against ulcerations in ethanol induced ulcer models indicate gastroprotective action by extracts of Trachyspermum ammi.

REFERENCES

1. Najm, WI (September 2011). "Peptic ulcer disease.". Primary care. 38 (3): 383–94, vii. PMID 21872087. doi:10.1016.j.pop.2011.05.001.
2. Milosavljevic, T; Kostić-Milosavljević, M; Jovanović, I; Krstić, M (2011). "Complications of peptic ulcer disease.". Digestive diseases (Basel, Switzerland). 29 (5): 491–3. PMID 22095016. doi:10.1159.000331517.
3. Steinberg, KP (June 2002). "Stress-related mucosal disease in the critically ill patient: risk factors and strategies to prevent stress-related bleeding in the intensive care unit.". Critical Care Medicine. 30 (6 Suppl): S362–4. PMID 12072662. doi:10.1097. 00003246-200206001-00005.
4. Wang, AY; Peura, DA (October 2011). "The prevalence and incidence of Helicobacter pylori-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world.". Gastrointestinal endoscopy clinics of North America. 21 (4): 613–35. PMID 21944414. doi:10.1016.j.giec.2011.07.011.
5. GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators. (8 October 2016). "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.". Lancet. 388 (10053): 1545–1602. PMC 5055577 .. PMID 27733282. doi:10.1016.S0140-6736(16)31678-6.
6. GBD 2015 Mortality and Causes of Death, Collaborators. (8 October 2016). "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015.". Lancet. 388(10053): 1459–1544. PMC 5388903 .. PMID 27733281. doi:10.1016.s0140-6736(16)31012-1.
7. "Definition and Facts for Peptic Ulcer Disease". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 28 February 2015.

8. Rao, S. Devaji (2014). Clinical Manual of Surgery. Elsevier Health Sciences. p. 526. ISBN 9788131238714.
9. "Eating, Diet, and Nutrition for Peptic Ulcer Disease". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 28 February 2015.
10. Snowden FM (October 2008). "Emerging and reemerging diseases: a historical perspective". Immunol. Rev. 225 (1): 9–26. PMID 18837773. doi:10.1111.j.1600-065X.2008.00677.x.
11. GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.". Lancet. 385: 117–71. PMC 4340604 .. PMID 25530442. doi:10.1016.S0140-6736(14)61682-2.
12. "The Nobel Prize in Physiology or Medicine 2005". nobelprize.org. Nobel Media AB. Retrieved 3 June 2015.
13. Bhat, Sriram (2013). SRB's Manual of Surgery. p. 364. ISBN 9789350259443
14. "Peptic Ulcer". Home Health Handbook for Patients & Caregivers. Merck Manuals. October 2006.
15. "Peptic ulcer". Retrieved 18 June 2010.
16. "Ulcer Disease Facts and Myths". Retrieved 18 June 2010.
17. Cullen DJ; Hawkey GM; Greenwood DC; et al. (1997). "Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs". Gut. 41 (4): 459–62. PMC 1891536 .. PMID 9391242. doi:10.1136.gut.41.4.459.
18. http:..www.uptodate.com.contents.association-between-helicobacter-pylori-infection-and-duodenal-ulcer
19. "antral mucosa - Humpath.com - Human pathology". web.archive.org. Archived from the originalon 2011-11-09. Retrieved 27 February 2014.
20. "Stomach ulcer - Causes - NHS Choices". www.nhs.uk. NHS.
21. Fink, G (February 2011). "Stress controversies: post-traumatic stress disorder, hippocampal volume, gastroduodenal ulceration*.". Journal of neuroendocrinology. 23 (2): 107–17. PMID 20973838. doi:10.1111.j.1365-2826.2010.02089.x.
22. Yeomans, ND (January 2011). "The ulcer sleuths: The search for the cause of peptic ulcers.". Journal of Gastroenterology and Hepatology. 26 Suppl 1: 35–41. PMID 21199512. doi:10.1111.j.1440-1746.2010.06537.x.
23. For nearly 100 years, scientists and doctors thought that ulcers were caused by stress, spicy food, and alcohol. Treatment involved bed rest and a bland diet. Later, researchers added stomach acid to the list of causes and began treating ulcers with antacids. National Digestive Diseases Information Clearinghouse
24. Ryan-Harshman, M; Aldoori, W (May 2004). "How diet and lifestyle affect duodenal ulcers. Review of the evidence.". Canadian Family Physician. 50: 727–32. PMC 2214597 .. PMID 15171675.
25. Pennsylvania, Editors, Raphael Rubin, M.D., Professor of Pathology, David S. Strayer, M.D., Ph.D., Professor of Pathology, Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University Philadelphia, Pennsylvania ; Founder and Consulting Editor, Emanuel Rubin, M.D., Gonzalo Aponte Distinguished Professor of Pathology, Chairman Emeritus of the Department of Pathology and Cell Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia,. Rubin's pathology : clinicopathologic foundations of medicine (Sixth Edition. ed.). Philadelphia: Wolters Kluwer Health.Lippincott Williams & Wilkins. p. 623. ISBN 978-1605479682.
26. Salih, Barik; M Fatih Abasiyanik; Nizamettin Bayyurt; Ersan Sander (June 2007). "H pylori infection and other risk factors associated with peptic ulcers in Turkish patients: A retrospective study". World Journal of Gastroenterology. 13 (23): 3245–8. PMID 17589905.
27. A, Sonnenberg; Müller-Lissner SA; Vogel E; Schmid P; Gonvers JJ; Peter P; Strohmeyer G; Blum AL (1981). "Predictors of duodenal ulcer healing and relapse.". Journal of Gastroenterology. 81 (6): 1061–7. PMID 7026344.
28. Lanas, A; Chan, FK (23 February 2017). "Peptic ulcer disease.". Lancet. PMID 28242110. doi:10.1016.S0140-6736(16)32404-7.
29. Perry, RR; Feliberti, E; Vinik, A; De Groot, LJ; Chrousos, G; Dungan, K; Feingold, KR; Grossman, A; Hershman, JM; Koch, C; Korbonits, M; McLachlan, R; New, M; Purnell, J; Rebar, R; Singer, F; Vinik, A (November 28, 2013). "Gastrinoma Zollinger-Ellison-Syndrome". Endotext. PMID 25905301.
30. http:..www.merckmanuals.com.professional.gastrointestinal-disorders.gastritis-and-peptic-ulcer-disease.peptic-ulcer-disease
31. "Peptic ulcer". Retrieved 18 June 2010.
32. "Tests and diagnosis". Retrieved 18 June 2010.
33. "ATLAS OF PATHOLOGY". Retrieved 26 August 2007.
34. "WHO Disease and injury country estimates". World Health Organization. 2009. Retrieved 11 November 2009.
35. Brown LM (2000). "Helicobacter pylori: epidemiology and routes of transmission.". Epidemiol. Rev. 22 (2): 283–97. PMID 11218379. doi:10.1093.oxfordjournals.epirev.a018040.
36. "Peptic ulcer disease". Retrieved 18 June 2010.
37. Johannessen T. "Peptic ulcer disease". Pasienthandboka.
38. Rigas, Basil; Papavasassiliou, Efstathios D. (22 May 2002). "Ch. 7 John Lykoudis. The general practitioner in Greece who in 1958 discovered the etiology of, and a treatment for, peptic ulcer disease.". In Marshall, Barry J. Helicobacter pioneers: firsthand accounts from the scientists who discovered helicobacters, 1892–1982. John Wiley & Sons. pp. 74–88. ISBN 978-0-86793-035-1.
39. Marshall B.J. (1983). "Unidentified curved bacillus on gastric epithelium in active chronic gastritis". Lancet. 1 (8336): 1273–75. PMID 6134060. doi:10.1016.S0140-6736(83)92719-8.
40. Marshall B.J.; Warren J.R. (1984). "Unidentified curved bacilli in the stomach patients with gastritis and peptic ulceration". Lancet. 1 (8390): 1311–15. PMID 6145023. doi:10.1016.S0140-6736(84)91816-6.
41. Kathryn Schulz (9 September 2010). "Stress Doesn't Cause Ulcers! Or, How To Win a Nobel Prize in One Easy Lesson: Barry Marshall on Being ... Right". The Wrong Stuff. Slate. Retrieved 17 July2011.
42. Van Der Weyden MB, Armstrong RM, Gregory AT (2005). "The 2005 Nobel Prize in physiology or medicine". Med. J. Aust. 183 (11–12): 612–4. PMID 16336147.
43. "Ulcer, Diagnosis and Treatment - CDC Bacterial, Mycotic Diseases". Cdc.gov. Retrieved 27 February 2014.
44. Huwez FU, Thirlwell D, Cockayne A, Ala'Aldeen DA (December 1998). "Mastic gum kills Helicobacter pylori [Letter to the editor, not a peer-reviewed scientific article]". N. Engl. J. Med. 339(26): 1946. PMID 9874617. doi:10.1056.NEJM199812243392618. Retrieved 6 September 2008.See also their corrections in the next volume.
45. Loughlin MF, Ala'Aldeen DA, Jenks PJ (February 2003). "Monotherapy with mastic does not eradicate Helicobacter pylori infection from mice". J. Antimicrob. Chemother. 51 (2): 367–71. PMID 12562704. doi:10.1093.jac.dkg057.
46. Bebb JR, Bailey-Flitter N, Ala'Aldeen D, Atherton JC (September 2003). "Mastic gum has no effect on Helicobacter pylori load in vivo". J. Antimicrob. Chemother. 52 (3): 522–3. PMID 12888582. doi:10.1093.jac.dkg366.
47. USDA GRIN entry
48. ITIS entry for Trachyspermum ammi
49. definition of ajowan in Oxford dictionary (British & World English)
50. "Trachyspermum ammi". Natural Resources Conservation Service PLANTS Database. USDA. Retrieved 14 December 2015.
51. "Bishop's Weed". SPICES BOARD INDIA. Retrieved 14 August 2015
52. Green (January 2006). Field Guide to Herbs & Spices: How to Identify, Select, and Use Virtually Every Seasoning at the Market. Quirk Books. pp. 116–117. ISBN 978-1-59474-082-4.
53. Rajasthan Gov, Commissionerate of Agriculture.
54. Alan Davidson (2014). The Oxford Companion to Food. Oxford University Press. pp. 9–. ISBN 978-0-19-967733-7.
55. Bairwa, Ranjan; Rajawat, BS; Sodha, RS (2012). "Trachyspermum ammi". Pharmacognosy Reviews. 6 (11): 56. doi:10.4103.0973-7847.95871.
56. Singh, Gurdip; Maurya, Sumitra; Catalan, C.; de Lampasona, M. P. (June 2004). "Chemical Constituents, Antifungal and Antioxidative Effects of Ajwain Essential Oil and Its Acetone Extract". Journal of Agricultural and Food Chemistry. 52 (11): 3292–3296. PMID 15161185. doi:10.1021.jf035211c.
57. Kohda,K. et al. Role of apoptosis induced by Helicobacter pylori infection in the development of duodenal ulcer. Gut 1999; 44: 456-462.
58. Min,C., et al. Effects and mechanism of changes of local neurotransmitters in rats' pylorus and bile reflux to the stomach with stress ulcer. Dig. Dis. Sci 2005, 50: 1898-1903.
59. Hakan Dursun et al. Antiulcer activity of fluvoxamine in rats and its effect on oxidant and antioxidant parameters in stomach tissue. BMC Gastroenterology 2009, 9:36.
60. T. Sen et al. Effect of dothiepin on gastric ulceration mediated by lipid derived eicosanoids Life Sciences 2000; 66:23: 325-330.
61. Halis Suleyman et al. Comparative study on the gastroprotective potential of some antidepressants in indomethacin-induced ulcer in rats. Chemico-Biological: 2009; 180 ;2: 318-324.
62. Bickel M. Antiulcer effects of nomifensine, a new antidepressant, on stress-induced ulcers in the rat. Arzneimittelforschung. 1980; 30(1):69-73.
63. Makoto Saito,Hiroshi Hosoyama et al. Antiulcer Activity of Grape Seed Extract and Procyanidins. J. Agric. Food Chem., 1998, 46 (4), 1460–1464
64. Shailja sood et al. Activity of tacrolimus: An immunosuppressant, in pyloric ligation induced peptic ulcer in rats. Yakugaku Zasshi 2009, 129(12):1523-1528.
65. Freitas,C.S. et al. Involvement of nitric oxide in the gastroprotective effects of an aqueous extract of Pfaffia glomerata (Spreng) Pedersen, Amaranthaceae, in rats. Life Sci 2004; 74: 1167-1179.
66. Lanas, A.et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. N. Engl. J Med. 2004; 343: 834-839.
67. Dykhuizen,R.S.,et al. Helicobacter pylori is killed by nitrite under acidic conditions. Gut 1998; 42: 334-337.
68. Jones,M.K. et al. Gene therapy for gastric ulcers with single local injection of naked DNA encoding VEGF and angiopoietin-1. Gastroenterology 2001; 121:1040-1047.
69. Wozniak-Holecka, et al. Influence of vascular endothelial growth factor (VEGF) on gastroprotection in stress-induced gastric mucosal ulcers in rats. Methods Find. Exp Clin. Pharmacol. 2009; 31: 523-531.