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RESEARCH ARTICLE

Piper nigrum and *Ferula foetida* shows Significant Antisecretory and Anti Ulcer Activity in Rats

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ABSTRACT

In the present study, the gastroprotective mechanism of aqueous extract of *Piper nigrum* and *Ferula foetida* (AEPF) was investigated. In the current study AEPF showed significant anti ulcer activity in rats. The antiulcerogenic impact of the AEPF is also associated with its antisecretory action since acid may be a major consideration of the event of ulceration. The current data also clearly demonstrated that 400 mg/kg is more effective than 200 mg/kg and 100 mg/kg dose of AEPF and has shown increased pH and decreased total acidity of gastric fluid. The ulcerogenic effect of cysteamine-induced duodenal ulcers was developed in rats that received cysteamine HCl 400 mg/kg. The exact mechanism of pathological process within the cysteamine-induced peptic ulcer model is not totally known, but hypersecretion of gastric acid, deterioration of mucosal resistance, and promotion of gastric emptying are among the possible mechanisms. In cold restraint stress-induced ulcer model, blood parameters such as glucose, cholesterol, and triglycerides were estimated. The significant increase in blood sugar level was discovered because, beneath nerve-racking conditions, ductless gland secretes corticosterone in man and glucocorticoid in rats. AEPF significantly reduced the elevated serum cholesterol and triglycerides levels, which may be due to inhibition of stimulation of the sympathetic nervous system. Therefore, it could act as a potent therapeutic agent against peptic ulcer disease.

Keywords: Antisecretory activity, *Piper nigrum*, *Ferula foetida* immobilization stress, ulcer activity

INTRODUCTION

Medicinal plants are reservoir of drugs and lead compounds for many therapeutic agents.[1] There is avalanche of scientific support on the efficacy of medicinal plants in the treatment of gastrointestinal disorders and in the management of ulcers of different etiologies.[2,3]

Peptic ulcer may be a conglomerate of heterogeneous disorders, which manifests itself as a break in the lining of the gastrointestinal mucosa bathed by acid and/or pepsin. Nonsteroidal anti-inflammatory drug (NSAID) ingestion is associated with erosions, petechiae, Type C gastritis, ulceration, interference with ulcer healing, ulcer complications, and injury to the small and large intestine.[4] Although a number of antiulcer drugs such as H2 receptor antagonists, proton-pump inhibitors, and cytoprotectants are available for ulceration, all these drugs have side effects and limitations.[5] Ethanol easily and rapidly penetrates into the gastric mucosa.[6] By increasing mucosal permeability and unleash of vasoactive merchandise, ethanol causes vascular damage and gastric cell necrosis, which, in turn, leads to ulcer formation.[7]

There is a balance in the stomach between the aggressive digestive capabilities of acid plus pepsin and the mucosal barrier. Ulceration happens once there is a disturbance of the traditional equilibrium caused by either increased aggression or diminished membrane resistance. Several factors are involved within the pathological process of peptic ulcer. These embrace multiplied acid-pepsin secretion, impaired bicarbonate neutralization, impaired mucous secretion, and precipitate lesions on the mucosal layer.[8] Acid and pepsin secretion must be considered together because in practice it is difficult to distinguish the effects of each alone.[9] Drug treatment of

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biological process ulcers is targeted at either counteracting aggressive factors (acid and enzyme, active oxidants, platelet-activating factor, leukotrienes, endothelins, and bile or exogenous factors including NSAIDs) or stimulating the mucosal defenses (mucus, bicarbonate, normal blood flow, prostaglandins, and nitric oxide).[10]
The ideal aims of the treatment of peptic ulcer disease are to relieve pain, heal the ulcer, and delay ulcer recurrence.[11]
In Western countries, the prevalence of *Helicobacter pylori* infections roughly matches age (i.e., 20% at age 20, 30% at age 30, and 80% at age 80). The prevalence is higher in the third world countries. Transmission is by food, contaminated groundwater, and through human saliva (such as from kissing or sharing food utensils).
A minority of cases of *Helicobacter* infection can eventually cause ulceration and a bigger proportion of individuals can get non-specific discomfort, abdominal pain, or rubor.
The methods used to assess the epidemiology of ulcers include hospital data, mortality statistics, population studies, and sickness benefit records. All of these methods have limitation and make comparative studies difficult.

MATERIALS AND METHODS

Plant material

The plant material of *Piper nigrum* and *Ferula foetida* was collected from the medicinal plants farm, Mulugu, Warangal district surroundings Telangana state. The material was taxonomically known and authenticated by Mr. P. V. Prasanna, Scientist "E"/Officer In-charge, BSI, Government of India and the voucher specimen No. BSI/DRC/2014-2015/Tech/746.

Extraction/fractionation procedure

The material of *P. nigrum* and *F. foetida*[12] is ground to coarse type and this dried powder was used for extraction. Extraction was done by maceration process. Take ingredients in the round bottom flask; add sufficient water to the round-bottom flask as solvent. Equal quantity of crude drug (50 g each) in 1000 ml water is taken for maceration process. The whole equipment was unbroken aside for 3–4 days. In-between completely, the solvent was mixed for higher extraction. After 4 days, the contents were filtered and marc was separated.[13]
Further, concentration of the extract was created by heating and evaporating the solvent unbroken in an exceedingly water tub at 400°C, which finally gave a dark sticky residue. It was stored in an airtight container in a refrigerator.

Experimental animals

Albino rats of Wistar strain of either sex weighing 150–200 g were taken for the study and housed under standard conditions (room temperature 24–270°C and humidity 60–65%) with 12 h light and dark cycle. The animals were provided food in the form of dry pellets and water was ad libitum. The animals were fasted before the experiment as per the method. Experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Malla Reddy College of Pharmacy, Hyderabad, with protocol no. MRCP/IAEC/1217/PCOL/3.

Preliminary phytochemical screening

Preliminary phytochemical screening was done for the presence of carbohydrates, proteins, saponins, alkaloids, flavonoids, tannins, triterpenoids, and phenolic compounds according to the procedures described in "Text book of Practical Pharmacognosy" by C. K. Kokate.

Treatment schedule

1. Control group (No pylorus ligation) – these rats received 1 ml distilled water.
2. Control group (With pylorus ligation) – these rats received 1 ml distilled water.
3. Positive control – aspirin (200 mg/kg p. o) + Pylorus ligation.
4. Standard – omeprazole (10 mg/kg p. o) + aspirin (200 mg/kg p. o) + pylorus ligation.
5. Graded doses of aqueous extract of *Piper nigrum* and *Ferula foetida* (AEPF-(100, 200, and 400 mg/kg, p. o.) and its aspirin (200 mg/kg, p. o.) were tested Against pylorus ligation model to identify the effective dose and selected to further studies in other ulcer models.

In this technique, anomaly rats were fasted in individual cages for 24 h. Care was taken to avoid coprophagy. Aspirin was administrated orally in the dose of 200 mg/kg in non-fasted rats once daily for 5 days. Test drug and omeprazole were administrated orally to respective treatment groups 30 min before each aspirin treatment, whereas the control received only distilled water. On the 6th day, pylorus ligation was performed under ether anesthesia on 36 h fasted rats, immediately after pylorus ligation aspirin treatment was given. Drinking water was withheld when porta tying on the 6th day in every rat and digestive fluid was allowed to accumulate for the amount of 4 h. At the top of 4 h when tying, the animals were sacrificed with an excess of anesthetic ether, and the stomach was dissected out. Gastric juice was collected and its volume was measured. The organ portion was then exposed and examined for ulceration. Ulcer index was determined.

Cysteamine-induced duodenal ulceration

Albino rats were selected and square measure classified into six teams of six animals every.

- Group I: Management – these rats received 1 ml water.
- Group II: Positive control cysteamine (400 mg/kg p. o.).
- Group III: Standard – omeprazole (10 mg/kg p. o.) + cysteamine (400 mg/kg p. o.).
- Group IV: AEPF one (100 mg/kg p. o.) + cysteamine (400 mg/kg p. o.).
- Group V: AEPF a pair of (200 mg/kg p. o.) + cysteamine (400 mg/kg p. o.).
- Group VI: AEPF three (400 mg/kg p. o.) + cysteamine (400 mg/kg p. o.).

Experimental procedure

Cysteamine HCl (400 mg/kg, p. o. in 100% liquid solution) was administered in two doses at an interval of 4 h to cause small intestine ulcers in rats. The extract was given daily for 5 days. Extract or reference drug or control vehicle was administered 30 min before each dose of cysteamine HCl. All the animals were sacrificed after 24 h when the primary dose of cysteamine was administered. Then, duodenum was excised carefully and opened along the antimesenteric side. The ulceration score was obtained by the size of the small intestine ulceration(s) in square millimeters which determines the ulcer index.

Cold restraint stress-induced ulcers

Albino rats were selected and are grouped into six groups of six animals each.

- Group I: Control – these rats received 1 ml distilled water.
- Group II: Positive control.
- Group III: Standard – omeprazole (10 mg/kg p. o).
- Group IV: AEPF 1 (100 mg/kg p. o).
- Group V: AEPF 2 (200 mg/kg p. o).
- Group VI: AEPF 3 (400 mg/kg p. o).

Experimental procedure

Animals were fasted for 24 h before the experiment and divided into six teams with six animals in every cluster. Extract was given daily for 5 days. On the past day after the administration of control vehicle or test drug or reference drug, stress ulcers were induced after 30 min of extract or omeprazole treatment; rats were immobilized under light ether anesthesia and subjected to the cold stress at 4 ± 1°C for 3.5 h.[13] The rats were sacrificed when 3 h when the cold restraint stress. Blood was collected by artery hemorrhage, allowed to stay at room temperature for some time, and then centrifuged at 4000 rpm for 15 min. Serum was separated from centrifuged blood and stored for estimation of serum biochemical parameters, i.e., glucose, triglycerides, and cholesterol. The animals were sacrificed beneath lightweight ether physiological condition; the abdomen of every animal was removed and cut on the bigger curvature. The extent of gastric damage was assessed. Ulcer index and percentage ulcer inhibition were calculated.

Statistical analysis

The applied math analysis was dispensed victimization unidirectional analysis of variance followed by Dunnett's multiple comparisons for the info that square measure commonly distributed. For the data of ordinal type, a non-parametric test was used. Kruskal–Wallis one-way analysis of variance was computed for overall significance and for observing significant difference. All the results obtained within the study were compared

with the vehicle management cluster. The *P* Values are expressed as mean ± SEM. Data analysed by one way ANOVA followed by dunnet's multiple comparision test. ***$P < 0.001$ **$P < 0.01$, *$P < 0.05$ when compare to the standard drug treated groups.

RESULTS

According to the phytochemical analysis showed the presence of carbohydrates, Phenolic compounds, Acidic compounds, Volatile oils, Fats/oils, Resins ,sterols. It was noticed that tannins, alkaloids, saponins, flavonoids were found in the extracts of *Piper nigrum* and *Ferula foetida* [Table 1].

DISCUSSION

The pyloric ligature model showed vital reduction in basal stomach secretion and inhibition of ulcers by liquid extract of *P. nigrum* and *F. foetida* (AEPF). This suggests that the antiulcer activity of AEPF on gastric mucosa may be due to the reduction of gastric secretion through one or more of the possible mechanisms.[14] Moreover, internal organ acid is a vital issue for the genesis of ulcerationation in orifice ligature ulcer in rats. Gastric acid secretion is regulated by several factors together with anxiety, pneumogastric activity, cholinergic, histaminergic and gastrinergic neurotransmissions, the activities of various post-synaptic receptors, and the proton pump. It is so troublesome to elucidate the link between the mechanisms of the inhibition of internal organ acid by AEPF.

The antiulcer property of AEPF in porta ligature model is clear from its vital reduction in free acidity, total acidity, number of ulcers, and ulcer index showed in Table 2. AEPF-treated animals considerably smothered the formation of ulcers within the porta ligated rats and additionally shrunken each the concentration and enlarged the pH, it's steered that AEPF can suppress gastric damage induced by aggressive factors.[15]

The current knowledge is clearly incontestable that AEPF was smothered the aggressive issue, internal organ acid secretion. The antiulcerogenic impact of the AEPF could also be associated with its antisecretory action since acid could be a major consideration of the event of peptic ulceration. The current data also clearly demonstrated that 400 mg/kg is more effective than 200 mg/kg and 100 mg/kg dose of AEPF and has shown increased pH and decreased total acidity of gastric fluid.

The ulcerogenic impact of cysteamine is each fast and constant so providing a very reliable model for work the mechanism of small intestine ulcerogenesis and doable suggests that for its interference.[16] Our results confirmed the quality

Table 1: Preliminary phytochemical screening of aqueous extract of *Piper nigrum* and *Ferula foetida*

Chemical constituent	Result
Carbohydrates	++
Proteins	+
Amino acids	+
Glycosides	−
Saponins	+
Alkaloids	+
Tannins	+
Phenolic compounds	++
Steroids	–
Triterpenoids	++
Flavonoids	+
Acidic compounds	++
Volatile oils	++
Fats/oils	++
Resins	++

++: Abundantly found, +: Slightly found, −: Not found

Table 2: Effect of AEPF on aspirin plus pylorus ligation-induced gastric ulcer in rats

Groups	Treatment	Ulcer index mean±SEM	Total acidity (meq/lit)	Vol. of gastric juice (ml/100 g)
Group 1	No pylorus ligation (normal control)		-	-
Group 2	With only pylorus ligation (pylorus ligation control)	1.5±0.15*	55.50±3.81 *	1.95±0.076*
Group 3	Aspirin (200 mg/kg p.o.)+pylorus ligation (positive control)	3.0±0.11	83.166±1.55	2.21±0.11
Group 4	Omeprazole (10 mg/kg p.o.)+pylorus ligation	1.18±0.06***	49.50±1.17**	1.96±0.20**
Group 5	AEPF 1 (100 mg/kg p.o.)+aspirin (200 mg/kg p.o.)+pylorus ligation	1.86±0.15ns	42.667±6.67ns	2.217±0.152ns
Group 6	Extract 2 (200 mg/kg p.o.)+aspirin (200 mg/kg p.o.)+pylorus ligation	1.65±0.16**	40.983±0.643*	1.733±0.170ns
Group 7	Extract 3 (400 mg/kg p.o.)+aspirin (200 mg/kg p.o.)+pylorus ligation	1.59±0.27***	38.667±0.23 **	1.603±0.128*

Values are expressed as mean±standard error of the mean. Data analyzed by one-way analysis of variance followed by Dunnett's multiple comparison test. ***$P<0.001$ **$P<0.01$, *$P<0.05$ when compare to the aspirin-treated group. AEPF: Aqueous extract of *Piper nigrum* and *Ferula foetida*

of the strategy, so acute and almost invariably prominent duodenal ulcers were developed in rats that received cysteamine HCl 400 mg/kg showed in Table 3. The exact mechanism of pathologic process within the cysteamine-induced peptic ulcer model is not absolutely acknowledged; however, securement of internal organ acid, deterioration of membrane resistance, and promotion of internal organ removal are among the possible mechanisms.

Results additionally indicated that AEPF extract was effective with doses utilized in our study. For the most parameters together with ulceration space and ulceration index, the impact of larger doses of the extract was comparable the reference tested medicine. The exact mechanism of action could not be clearly painted; however, the candidate plant contains active materials that for many of them, ulceration protecting properties are steered. Anumber of attention-grabbing biological activities such as antiviral, antibacterial, anti-inflammatory, and antioxidant are attributed to this compound and a review on its pharmacology indicating a wide therapeutic potential including treating or preventing bronchial asthma, spasmogenic disorders, peptic ulcer, inflammatory disease, and atherosclerosis.[17] In addition, antiulcer drugs of plant origin show that triterpenoids due to their ability to strengthen defensive factors such as stimulation of mucus synthesis or maintenance of the prostaglandines level are potential compounds with antiulcer activity. In addition, by doing an acute toxicity test at doses up to 2000 mg/kg in mice, the safety of extract was confirmed.

Table 3: Effect of AEPF on cysteamine-induced duodenal ulceration

Treatment	Dose	Ulcer index
Control		2.5±0.16**
Positive control	Cysteamine 400 mg/kg	4.166±0.17
Standard	Omeprazole 10 mg/kg p.o.	1.33±0.19***
AEPF1	100 mg/kg p.o.	2.89±0.11ns
AEPF 2	200 mg/kg p.o.	2.5±0.17*
AEPF 3	400 mg/kg p.o.	1.65±0.12***

Values are expressed as mean±standard error of the mean. Data analyzed by one-way analysis of variance followed by Dunnett's multiple comparision test. ***P<0.001, **P<0.01, *P<0.05 and ns – no significance when compared to the cysteamine-treated group. AEPF: Aqueous extract of *Piper nigrum* and *Ferula foetida*

Table 4: Effect of AEPF on cold restraint stress-induced gastric ulcers

Treatment	Dose	Ulcer index
Control		2.5±0.17**
Positive control	Cold restraint stress 3.5h	4.56±0.99
Standard omeprazole	10 mg/kg p.o.	1.33±0.10***
AEPF1	100 mg/kg p.o.	3.52±0.13ns
AEPF 2	200 mg/kg p.o.	1.86 ± 0.11**
AEPF 3	400 mg/kg p.o.	1.56 ± 0.18***

Values are expressed as mean±standard error of the mean. Data analyzed by one-way analysis of variance followed by Dunnett's multiple comparision test. ***P<0.001, ** P<0.01, *P<0.05 and ns – no significance when compared to the cold restraint stress group. AEPF: Aqueous extract of *Piper nigrum* and *Ferula foetida*

The useful effects of various single-dose pre-treatments with liquid extract of *P. nigrum* and *F. foetida* (AEPF) in chronic restraint stress (CRS)-induced internal organ ulcers were recently incontestable. In this sense, the antiulcer properties AEPF were investigated *in vivo*, at the level of gastric mucosa. Here, experimental animals were supplemented with AEPF for 5 days.

In the gift study, the ulcer protective activity of AEPF was confirmed through CRS-induced gastric ulcers. A potent antiulcer activity of AEPF in rat gastric mucosa was also evidenced showed in Table 4.

In gift study, in cold restraint stress-induced ulcer model, blood parameters such as glucose, cholesterol, and triglycerides are estimated showed in Table 5. The significant increase in blood sugar level was determined because, underneath nerve-wracking conditions, endocrine gland secretes hydrocortone in man and glucocorticoid

Table 5: Effect of AEPF on blood parameters in cold restraint stress-induced gastric ulceration model

Groups	Glucose mg/dl	Cholesterol mg/dl	Triglycerides mg/dl
Control	78.03±0.088**	83.18±0.05*	87.49±3.65*
Cold stress control	102.9±0.082	99.00±0.02	182.65±1.88
Omeprazole	86.9±0.02***	60.1±0.06**	85.02±3.42**
Extract 100 mg/kg p.o	97.4±0.01ns	69.6±0.02ns	143.99±4.01ns
Extract 200 mg/kg p.o	92.99±0.2*	66.1±0.05*	95.25±3.79*
Extract 400 mg/kg p.o	90.9±0.02***	63.00±0.02**	87.43±1.55**

Values are expressed as mean±standard error of the mean. Data analyzed by one-way analysis of variance followed by Dunnett's multiple comparision test. ***P<0.001, **P<0.01, *P<0.05 and ns – no significance when compared to the cold restraint stress group. AEPF: Aqueous extract of *Piper nigrum* and *Ferula foetida*

in rats. Hypersecretion of hydrocortone helps in maintenance of internal physiological condition through the method of gluconeogenesis and lipogenesis. Pre-treatment with the AEPF further as reference customary drug considerably reduced the elevated aldohexose levels indicating their appetite suppressant impact on hyperactivity of endocrine gland and maintained the homeostatic mechanism.

The marked increase in humor sterol, triglycerides levels in stress-evoked animals is thanks to the stimulation of hypothalamic-pituitary axis and sympathetic system, leading to, liberation of endocrine and glucocorticosteroids, which inhibits the immune system. AEPF significantly reduced the elevated serum cholesterol and triglycerides levels, which may be due to inhibition of the stimulation of sympathetic nervous system.

CONCLUSION

- Black pepper (*P. nigrum*) is a flowering vine in the family Piperaceae, cultivated for its fruit, which is usually dried and used as a spice and seasonings. The fruit, referred to as a pepper once dried, is close to 5 mm (0.20 in) in diameter, redness once absolutely mature, and, like all drupes, contains a single seed. Peppercorns, and therefore the fine-grained pepper derived from grinding them, may be described simply as pepper or more precisely as black pepper (cooked and dried unripe fruit), green pepper (dried unripe fruit), and white pepper (dried ripe seeds).
- Asafoetida, belongs to the family Apiaceae, (*Ferula asafoetida*), (also known as devil's dung, stinking gum, asant, food of the gods, giant fennel, Jowani badian, hing, and ting) is the dried latex (gum oleoresin) exuded from the living underground rootstock or faucet root of many species of Ferula that could be a perennial herb (1–1.5 m high). The species is native to Afghanistan Mountains and area unit foreign to Asian country. Asafoetida features a pungent, unpleasant smell once raw, however in seared dishes, it delivers a sleek flavor, adore leeks.
- Based on the traditional claim, the present work is undertaken to assess the antiulcer activity of AEPF.
- The AEPF at a dose of 100 mg/kg, 200 mg/kg, and 400 mg/kg has significantly reduced the incidence of ulcers in aspirin plus pylorus ligation, cysteamine-induced ulcer, and cold restraint stress-induced ulcer models. The experimental results suggest that AEPF has significant antiulcer activity.
- The main chemical constituents that are found in the aqueous extract *P. nigrum* and *F. foetida* are carbohydrates, phenolic compounds, triterpenoids, volatile oils, acidic compounds, and resins which may be responsible for the antiulcer activity.
- With the availability of primary information, further studies can be carried out to establish its exact mode of action and the active principles involved in the said effects.

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