# GASTROPROTECTIVE EFFECTS OF CUSCUTA REFLEXA ON ASPIRIN-INDUCED PEPTIC ULCER

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## ABSTRACT

**Background:** Gastroprotective effects of cuscuta reflexa may be considered as alterative to many currently used anti peptic ulcer drugs. **Objective:** To explore the *in-vivo* gastroprotective activity and antiulcer potential of crude extract of the indigenous medicinal plant, Cuscuta reflexa, belonging to the plant family 'Convolvulace. **Methodology:** This experimental study was conducted from 1st March to 1st July 2015 at faculty of pharmacy and alternative medicine, Islamia Universty Bahawalpur.The antiulcer activity of Cuscuta reflexa (Cs.Cr) was investigated in aspirin-induced ulcer models. Wistar Albino rats were divided into six groups, each consisting of six animals. Control and intoxicated groups received normal saline at the dose of 8 ml/kg, standard group received Cimetidine (100 mg/kg) and the test groups received three different doses (30, 100 and 300 mg/kg) of Cs.Cr oraly individually for seven days, with subsequent administration of aspirin (200 mg/kg oraly) for two consecutive days. At the end of the experimental period, rats were anaesthetized and sacrificed. The stomach was removed and incised to collect the gastric juice for determination of pH and acidity. The stomach from each group was evaluated for ulcer index and percent protection. Afterwards, stomachs were weighed and samples preserved in 10% formalin for histopathological studies. Acute toxicity studies were also performed in mice. The extract (Cs.Cr) was also analyzed phytochemically for the presence of various secondary metabolites. **Results:** Oral administration of the crude extract of Cuscuta reflexa (Cs.Cr) exhibited dose-dependent (30-300 mg/kg) significant protection ($p<0.05$) in the Aspirin-induced peptic ulcerated animals. The extract, Cs.Cr, was found to be safe up to the dose of 10 g/kg in mice. Phytochemical analysis showed the presence of several metabolites like glycosides, flavonoids, saponins, terpenes and tannins in the crude extract of the plant. **Conclusion:** The results of the study clearly showed that Cs.Cr possesses gastroprotective potential and caused the reversal of peptic ulceration which justify the traditional use of the plant in several gastric ailments like hyperacidity, gastro-esophageal reflux disease and ulcer. However, further investigations are needed to explore the exact mechanism(s) responsible for protective effects of the plant.

**Key Words**: Cuscuta reflexa, Aspirin, Peptic Ulcer, Ulcer Index

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## INTRODUCTION

Peptic ulcer is a multifactorial disease distressing about 8-10% of the global population.[1] It is the erosion in the mucosa of stomach or duodenum and caused by the disruption of defense and repair mechanism of gastric mucosa.[2] The ulcer in stomach is known as gastric ulcer and that in duodenum is called duodenal ulcer and together it is termed as peptic ulcer.[3] Gastric ulcers are more common in the middle aged men especially associated with the chronic use of non-steroidal anti-inflammatory drugs, tobacco, alcohol and ischemic reperfusion.[4] The incidence of peptic ulcer increases with age. In the 5th decade of life, peak prevalence is 28.8% with the life time prevalence of 11.22%.[5] Currently available drugs used for the treatment of peptic ulcer include antacids, $H_2$ receptors antagonists, proton pump inhibitors and the drugs affecting the defensive mucosal barrier, but the major drawback of the gastric ulcer therapy is that the currently available drugs for peptic ulcer are associated with severe side effects such as headache, indigestion, sedation, confusion etc.[6] Natural products especially medicinal plants and/or herbs having folkloric and traditional uses have shown important role in the treatment of a number of gastrointestinal disorders.[6] Plant derived saponins,[7] tannins,[8] flavonoids,[8,9] essential oils,[10] gums and mucilages,[11] have received considerable attention in recent decades due to their miscellaneous pharmacological properties including antisecretory and gastroprotective activities.[6]

Cuscuta reflexa is a golden yellow, leafless, perennial parasitic herb of Convolvulaceae family, commonly known as Akashvalli, Akasbel or Dodder.[12] From mid-summer to early autumn, the vines can produce small fruit that take the same color as the vine.[13] The stems of the parasitic plant are very long and densely intermingled, light greenish yellow in color and occasionally red dots are present, seeds are glabrous, black in color and produced in large quantities.[14] *C.* reflexa has various medicinal uses that are reported including its anti-microbial activity, in loss of appetite, rheumatic arthritis, urinary

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disorders, splenomegaly, to strengthen body and hair, and as cholagogue.[15] The infusion of whole plant is used to wash sores, bilious disorders are treated by stems, fruits are used to treat fever and cough, cold infusions of seeds are used as depurative while stomach aches and pains are also treated by infusion of seeds.[16] The plant is pharmacologically reported to have antioxidant, anticonvulsant, diuretic, hepatoprotective, anti-inflammatory, anticancer, antisteroidogenic, antihypertensive and spasmolytic properties.[17] This study was conducted to assess in vivo gastroprotective activity and antiulcer potential of crude extract of cuscuta reflexa, belonging to plant family Convolvulace.

## METHODOLOGY

This experimental study was conducted from 1st March to 1st July 2015 in Department of Pharmacy and Alternative medicine, Islamia Universty Bahawalpur. Whole plant of Cuscuta reflexa was purchased from the local market after identification by the authentic botanist. The specimen was preserved in the herbarium of faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur, Pakistan, and voucher number (CR-WP-05-10-006) was issued for future reference. The whole plant of *C.* reflexa was washed, shade dried and screened to remove any extraneous material. The plant material was coarsely powdered and macerated with 70% methanolic water at room temperature for three day. The soaked material was first filtered through muslin cloth and then through filter paper. After three consecutive soakings and filtrations, the filtrates were evaporated at low temperature (30-40 °C) under reduced pressure by using rotary evaporator (Heidolph Laborota 4000 efficient, Germany). At the end of extraction process, the crude extract of plant (Cs.Cr) was obtained as thick viscous paste which was further dried in hot air oven at 40 °C and weighed as 28.5g .

### Preliminary Phytochemical Analysis

Cs.Cr was subjected to qualitative phytochemical analysis to study the presence of various secondary metabolites; alkaloids, glycosides, tannins, flavonoids, saponins etc. Foam test for Saponins, Ferric chloride test for Tannins, different tests for alkaloids such as Hager's test, Wagner's test, Dragendroff's test and Mayer's test, Keller-Killiani test for glycosides, Alkaline reagent and Lead acetate tests for flavonoids,[18] tests for coumarins, phlobatannins and quinones were performed.[19,20,21]

### Experimental Animals

Healthy Wistar albino rats (180-250 g) were used for this experimental study after approval by the Animals Research Ethics Committee, department of Pharmacy, faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur. All the experimental animals were housed in the animal house of Pharmacology and Physiology research laboratory at the faculty of Pharmacy and Alternative Medicine, IUB. The animals were kept in polycarbonate cages of size 47×34×18 $cm^3$ and were maintained under standard conditions of temperature (21-23 °C) and humidity (45-55%) along with exposure to 12:12 hours light and dark cycle. The animals were fed with standard diet and allowed to drink water *ad libitum* throughout the experimental period. They were acclimatized for 15 days before starting the study to minimize animal stress.

### Experimental Design:

### Animal Model

The animals were divided into five groups with 6 animals in each group. Intoxicated group received normal saline (8ml/kg, oraly), Treatment groups received the crude extract Cs.Cr in different doses (30mg/kg, 100mg/kg and 300mg/kg, oral and Standard control group received Cimetidine (100mg/kg, oraly) as the standard drug for comparison. All the treatments were given for seven days. After treatment period, the animals were kept fasted for 18-24 hours with free access to water before the induction of ulcer.

On 8th day, ulcer was induced by the administration of Aspirin (200mg/kg, oraly), to all groups except Control. Aspirin was again administered for another consecutive day. After 4 hours, the animals were anesthetized by using thiopentone sodium intraperitoneally and sacrificed. The abdomen was cut open by midline incision, cardiac and pyloric ends of the stomach were ligated with catgut and the stomach was removed. The stomach was incised along the greater curvature. The gastric contents were collected in centrifuge tubes.[19] The stomach was flushed with normal saline and examined for ulcer index. After gross examination, the tissue was preserved in 10% formalin for histopathological study.[20]

**Determination of Ulcer Index and percent Protection**

The ulcer index was calculated by adding the total number of ulcers per stomach and the total severity of ulcers per stomach. The severity of gastric ulcer score was noted as:

- No ulcer…0
- Changes limited to superficial layer of the mucosa with no congestion…1
- Half the mucosal thickness shows necrotic changes…2
- More than 2/3rd of the mucosal thickness shows necrotic changes…3
- Complete destruction of the mucosa with hemorrhage…4

The ulcer index (UI) was calculated as given below :

$UI = Un + Us + (Up \times 10^{-1})$

Un: Average number of ulcers per animal
Us: Average number of severity of scores, and
Up: Percentage of animals with ulcers

Percent protection was calculated as follows:
Percent Protection = (C-T/C) x 100
Where; C: Ulcer Index in Control group, and, T: Ulcer Index in Treated group

**Estimation of other parameters**

Gastric contents were centrifuged at 5000rpm for 5 minutes; the volume of the supernatant was expressed as ml/100gm body weight. The centrifuged samples were decanted and analyzed for gastric volume, pH and total acidity. pH of the supernatant was noted with the help of pH meter. 1ml of supernatant liquid was pipette out and diluted to 10ml with distilled water. The solution was titrated against 0.1N sodium hydroxide using phenolphthalein as indicator. It was titrated till the solution regained pink color, the volume of NaOH used to neutralize the acid was noted and total acidity was calculated. The stomachs were dissected out from the experimental animals for histopathological study.

**Histopathological Studies**

The isolated stomachs were embedded in paraffin, cut into 5 µm thick sections with the help of microtome by serial sectioning and stained with haematoxylin-eosin dye. The slides of stomach sections were examined under optical microscope with camera for histological changes; ballooning, degeneration, inflammation, apoptotic cells and fibrosis in stomach architecture, loss of nuclei and leukocyte infiltration. Their photomicrographs were also taken.

**Toxicity Studies**

Acute oral toxicity test was performed by following OECD guidelines. Swiss albino mice (18-30g) were randomly selected to determine mortality and behavioral changes of Cs.Cr in animals. The animals were divided into four groups each consisting of five mice; i.e. group I (control) received normal saline (10 ml/kg) orally. Group II, III and IV (test groups) received Cs.Cr at the different doses; 1 gm, 3 gm, 10 gm and 30 gm/kg of body weight, respectively. Different responses; i.e. touch response, pain response, urination, sweating, writhing reflex, hyperactivity, dizziness, convulsions, righting reflex and fever were observed at 0minutes, 30minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 1day, 2 day, 1week and 2 weeks after oral administration of Cs.Cr. The experimental animals received food and tap water ad libitum during study period.

**Statistical Analysis**

The results were analyzed statistically and expressed as Mean±S.E.M. One Way Analysis of Variance (ANOVA) with Bonferroni's test was used to compare all pairs of columns using GraphPad Prism Software to observe the significance levels between intoxicated, standard and test groups. P value >0.05 was considered as non-significant (ns), P<0.05 as significant (*), P<0.01 as more significant (**) and P< 0.001 as highly significant (*** or ###).

## RESULTS

**Preliminary Phytochemical Analysis**

The phytochemical analysis of the crude extract of Cuscuta reflexa (Cs.Cr) showed the presence of several secondary metabolites; saponins, glycosides, flavonoids, carbohydrates and terpenes; while, rest of the constituents were absent. The results of preliminary phytochemical analysis are given in Table I.

**Effects Cs.Cr on pH of gastric juice**

The crude extract of Cuscuta reflexa (Cs.Cr) was found to increase the pH of gastric juice in treated groups in a dose-dependent manner. The value of pH in group II (Intoxicated group) 3.897±0.149 was decreased as compared to that (4.8333±0.0628) of Control group. The pH of gastric contents in treatment group given Cs.Cr at the dose of 30mg/kg was 4.042±0.0952 which was found to be non-

significantly increased; whereas, pH values in Treatment groups given 100 and 300 mg/kg of Cs.Cr were noted as 4.920±0.0478 and 5.375±0.142 respectively. pH of gastric juice in Cimetidine treated group was the highest; i.e. 7.260±0.349 and was comparable treatment groups. The animals of Intoxicated group showed marked increase in total acidity of gastric contents. Oral administration of Cs.Cr showed a marked increase in pH of gastric contents when compared with Intoxicated group. (Figure I).

**Table I: Preliminary Phytochemical Constituents present in the crude extract of Cuscuta reflexa (Cs.Cr).**

| Phytochemical Tests | Phytochemical Constituents |
|---|---|
| **Saponins** | + |
| **Tannins** | - |
| **Alkaloids** | + |
| **Glycosides** | |
| Keller-killiani Test | + |
| **Flavonoids** | |
| i) Alkaline Reagent Test | + |
| ii) Lead Acetate Test | + |
| **Aminoacids and Proteins** | |
| i) Xanthoproteic Test | - |
| ii) Ninhydrin Test | - |
| **Carbohydrates** | |
| Fehling 's Test | - |
| ii) Benedict's Test | - |
| iii) Molisch's Test | + |
| **Coumarins** | + |
| **Phlobatannins** | - |
| **Quinones** | + |
| **Phenols** | + |
| **Terpenes** | |
| i) Salkowski's Test | - |
| ii) Copper Acetate Test | - |

**(Note: + sign indicates the presence and – sign indicates the absence; and number indicates the intensity)**

### Effects of Cs.Cr on Aspirin-induced Mucosal Lesions; i.e. Number and Severity of Scores

The effects of aqueous methanolic crude extract of Cuscuta reflexa (Cs.Cr) on aspirin-induced mucosal lesions in stomach are shown in Figure II. Mean value of number of scores in intoxicated group was calculated as 1.333±0.210. The value was found to be decreased in Cs.Cr (30 mg/kg) treated group; i.e. 1.183±0.116. Mean values of severity of scores in Cs.Cr (100 and 300 mg/kg) treated groups were calculated as 0.833±0.076 and 0.666±0.076. Standard (Cimetidine) group showed a marked decrease in the number of lesions i.e. 0.500±0.025. Pretreatment with Cs.Cr showed a marked decrease in number of lesions in treatment groups when compared with intoxicated group. The results were also compared with standard group. P value was found to be statistically significant; i.e. $P<0.05$ in treatment groups when compared with Intoxicated group. The P value was highly significant ($P<0.001$) of the standard group. The effects of Cs.Cr on Aspirin-induced mucosal lesions in stomach are shown in Figure III. Mean value of scores in Intoxicated group was 2.667±0.210. The value was found to be decreased in Treatment groups dose-dependently; i.e. 1.667±0.333 at the dose of 30mg/kg and 1.167±0.1667 and 0.833±0.1667 at the doses of 100 and 300mg/kg respectively. Standard group (Cimetidine) showed a marked decrease in mucosal lesions; i.e. 0.500. Pretreatment with Cs.Cr exhibited marked protective effect ($P<0.05$) when compared with intoxicated group. The results were also compared with standard group. The results obtained were in par with the standard group.

**Figure I: The graph showing the dose-dependent effects of the aqueous methanolic crude extract of Cuscuta reflexa (Cs.Cr) and the standard drug, Cimetidine, on pH of gastric contents. All the treatments are continued for seven days before two consecutive days treatment with Aspirin (200 mg/kg, oral).**

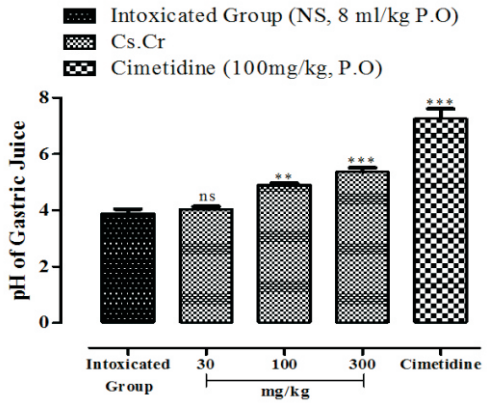



**Figure II: The graph showing the dose-dependent effects of the aqueous methanolic crude extract of Cuscuta reflexa (Cs.Cr) and Cimetidine, the standard anti-ulcer drug, on number of ulcers. The values are expressed as Mean±S.E.M of 4-6 observations. The values are expressed as Mean±S.E.M of 4-6 observations. All the treatments are continued for seven days before two consecutive days treatment with Aspirin (200**

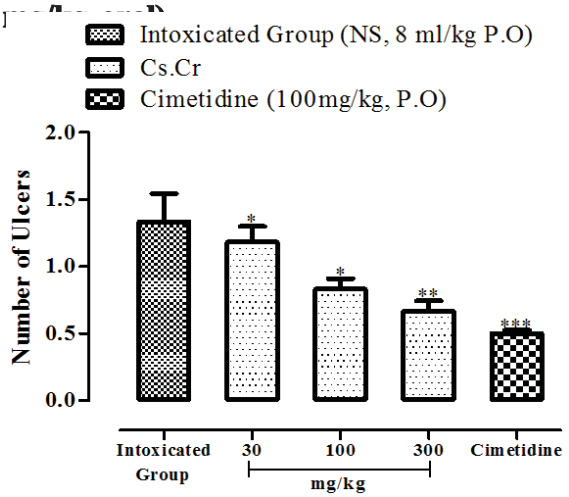
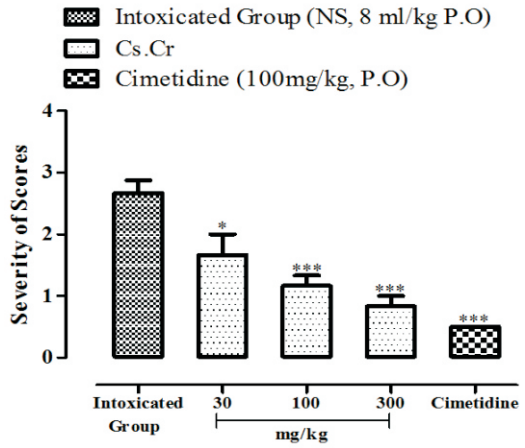



**Figure III: The graph showing the dose-dependent effects of the aqueous methanolic crude extract of Cuscuta reflexa (Cs.Cr) and Cimetidine on severity of ulcer scores. The values are expressed as Mean±S.E.M of 4-6 observations. All the treatments are continued for seven days before two consecutive days treatment with Aspirin (200 mg/kg, oral)**




## The Effects of Cs.Cr on Ulcer Index

Oral administration of aspirin solution produced characteristic mucosal damage which was evidenced by severity of lesions in intoxicated group. Pretreatment with Cs.Cr (seven days of treatment) caused a significant protective effect against aspirin-induced mucosal lesions. Ulcer indices in treatment groups were calculated as 11.86 at the dose of 30 mg/kg of Cs.Cr, 9.40 at 100 mg/kg and 7.49 at 300 mg/kg, which were compared with that of intoxicated group. The ulcer index in standard control group which received Cimetidine 100 mg/kg was calculated as 4.39. The extract was found to decrease the ulcer index in a dose-dependent manner as shown in Figure IV.

**Figure IV: The graph showing the dose-dependent effects of the aqueous methanolic crude extract of *Cuscuta reflexa* (Cs.Cr) and the standard drug, Cimetidine, on Ulcer Index. The values are expressed as Mean±S.E.M of 4-6 observations. All the treatments are continued for seven days before two consecutive days treatment with Aspirin (200 mg/kg, oral).**

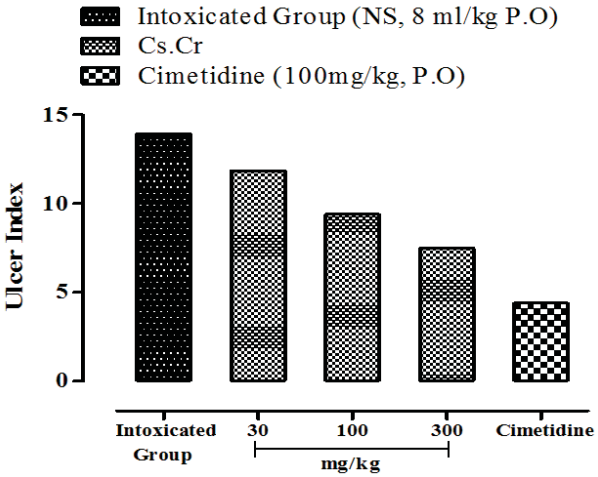
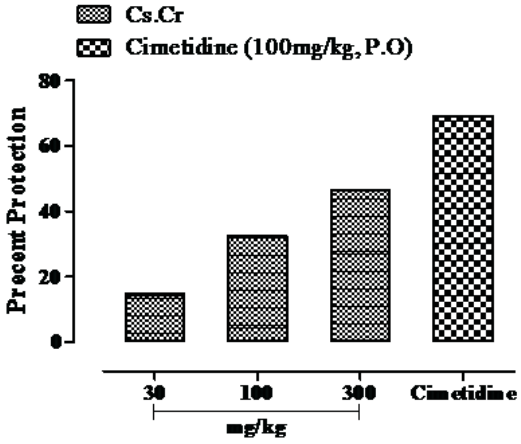



**Figure V: The graph showing the dose-dependent effects of the aqueous methanolic crude extract of Cuscuta reflexa (Cs.Cr) and the standard drug, Cimetidine, on Percent Protection. All the treatments are continued for seven days before two consecutive days treatment with Aspirin (200 mg/kg, oral).**

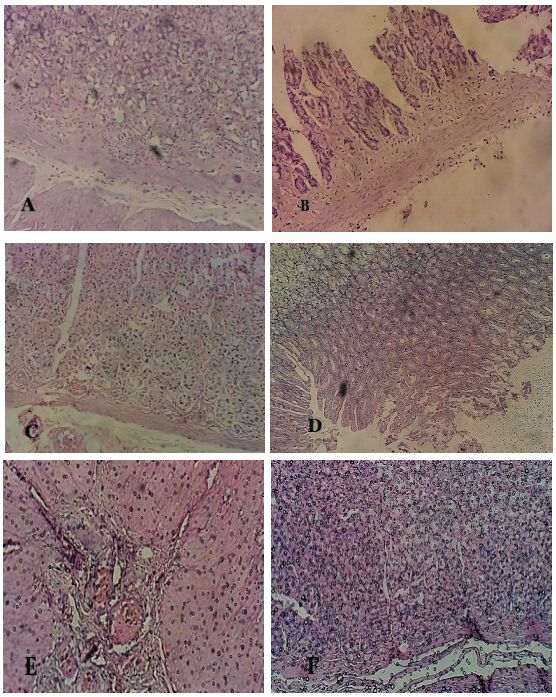



## The Effects of Cs.Cr on Percent Protection

The effects of Cs.Cr were also observed for the improvement in percent protection of mucosal injury caused by two consecutive days treatment of Aspirin (200mg/kg, oral. At the dose of 30 mg/kg of Cs.Cr, the percent protection was calculated as 14.92%, 32.56% at the dose of 100 mg/kg and 46.26/at the dose of 300mg/kg. The percent protection in

Cimetidine-treated group was found to be the highest; i.e. 69.15%. Cs.Cr was found to increase the percent protection in different groups in a dose-dependent fashion which showed that the extract increased mucosal resistance and regulated mucosal reconstitution. The results have been elaborated in Figure V.

**Figure V1: Figure showing micrographic (100X) results of slides of liver sections of different groups: (A) the control group, (B) extensive ballooning, inflammation, leukocyte infiltration, necrosis and highly degeneration of gastric mucosa in Aspirin-intoxicated group, (C) protective effects on stomach mucosa exerted by the standard drug, Cimetidine (100 mg/kg), and (D, E and F) showing the dose-dependent effects of Cs.Cr; 30, 100, and 300 mg/kg, respectively.**




### Histopathological Studies

Pretreatment of animals with the standard drug, Cimetidine (100 mg/kg) and the crude extract of Cuscuta reflexa, Cs.Cr at three different doses; 30, 100 and 300 mg/kg of body weight, decreased the hemorrhagic lesions of gastric mucosa, necrotic tissue and heavy infiltration (Figure 6D, 6E and 6F) as compared to that in Intoxicated group shown in FigureVI.

### Acute Toxicity Study

Cs.Cr was found to be safe upto 10 g/kg of body weight of mice with no behavioral changes observed for 14 days.

## DISCUSSION

Peptic ulcer is considered as a major gastrointestinal complication that is mainly attributed to discrepancies between defensive and offensive mechanisms.[22] There are number of pharmacological approaches which are available to cope with such invasive gastrointestinal disorders including cytoprotectives, prostaglandin analogues, antacids, $H_2$-receptor antagonists and proton pump inhibitors, but all these agents have their characteristic side effects and complications that hinder their frequent use.[23] Hence, natural products, especially plants' derived chemicals are considered as promising source of the development of new agents with safe therapeutic window.[24] Aspirin belongs to a well-known group of drugs, i.e. non-steroidal anti-inflammatory drugs (NSAIDs), which can cause peptic ulcer. This effect is attributed to their ability to inhibit the synthesis of prostaglandins.[25] The prostaglandins' synthesis is catalyzed by a group of enzymes called Cyclooxygenases. These enzymes are the prime target of NSAIDs.[26] Prostaglandins have a diverse actions on body and in stomach, they are responsible for many vital roles like maintaining mucosal blood flow, stimulating the secretion of bicarbonate and mucus and regulating mucosal cell turnover and repair.[27] Thus, inhibition of cyclooxygenase (especially COX-1) results in an increased susceptibility of gastric mucosa towards injury and lesions.[28] In this model, Cs.Cr exhibited a significant protection against mucosal damage in the aspirin-induced peptic ulcer model. These results suggest the possible involvement of prostaglandins and/or mucus in the antiulcer effect of the plant extract.[28] The presence of flavonoids and saponins have been found to exhibit antiulcer activities in various experimental models.[29] Gastroprotective effects of flavonoids have been justified by various mechanisms; which include increase of mucosal prostaglandin synthesis, decrease of histamine secretion from mast cells by inhibition of histidine decarboxylase and inhibition of Helicobacor pylori growth.[30] Moreover, flavonoids have been reported to be free radical scavenger; free radicals possess an important role in ulcerative and erosive lesions of gastrointestinal tract.[31] So, the antiulcer activity of Cs.Cr may be credited to its flavonoids content. Based on this data, it is suggested that the

gastroprotection observed in this study could be related to the presence of flavonoids in the plant, *Cuscuta reflexa.* In addition, histopathological effects confirmed the reservation of histo-architecture towards normal following dose-dependent fashion which suggested the protective effects.

## CONCLUSION

It is concluded from the results of the study that *Cuscuta reflexa,* frequently used in traditional medicine, exhibited protective effects on the gastric mucosa against aspirin-induced peptic ulcer in rats as indicated by marked reduction in the aspirin-induced ulcer index and marked elevation of pH of gastric contents. In addition, histopathological findings also supported the results of the crude extract Cs.Cr in causing gastroprotection. Cs.Cr was also found to contain several secondary metabolites; saponins, flavonoids, terpenes etc. which may be responsible for causing defense against ulceration of GI mucosa. Hence, the study justifies the traditional uses of the plant against various gastrointestinal disorders. However, further studies are required to be carried out to isolate the purified compound(s) and to explore the possible mechanism(s) responsible for the gastroprotective potential of the plant.

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