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# Pharmacological Evaluation of Antiulcer activity and potential mechanism of action of ethanolic extract of rhizome of kutaki (*Picrorhiza kurroa*)

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**Abstract**

HPLC was performed to evaluate the rhizome in order to verify the chemical composition of the Picrorhiza kurooa rhizome extract. Based on the acute toxicity research in Wister rats, which were used in this examination, the ability to provide stomach protection was examined at various dosages of 1, 5, 10, 15, and 50 mg/kg. The degree of gastric protection was determined using a number of metrics, including stomach volume, pH, total acidity, free acidity, ulcer index, and % inhibition of ulceration. The preferred drug was ranitidine *Picrorhiza kurrooa* ethanolic extracts 20 mg/kg reduced stomach volume, total acidity, and free acidity significantly ($P< 0.001$). However, with a dosage of 50 mg/kg, the pH of the gastric juice rose considerably ($P<0.001$). A substantial ($P< 0.001$) reduction in the number of ulcers was also observed. As a result, phytochemicals such flavonoids, saponins, alkaloids, and tannins found in plant extracts may be responsible for the extracts' antiulcer actions.

**Key Words**: Picrorhiza kurroea, peptic ulcer, pylorus ligation, gastric protection

## Introduction

As a result of oxidative stress, ulcers is a disease condition that develop when there is an imbalance between the aggressive forces (acid and pepsin) and mucosal protection factors (mucous, bicarbonate, and prostaglandins) . According to the pathophysiology of ulcers, non-steroidal anti-inflammatory medications (NSAIDs) and Helicobacter pylori are the main causes of ulcers. [1]. Actinomyces and NSAIDs damage the mucus lining of the stomach by a mechanism of inflammation, exposing the stomach's interior to acid, which irritates the tissue and results in peptic lesions [2–3]. When the proper techniques for its identification have been used, it has been discovered that nearly all, patients with duodenal and gastrojejunal ulcers exhibit an excessive secretion of gastric juice both when the stomach is fasting and in reaction to the consumption of food. Studies on experimental animals and observations of patients with peptic ulcers who had complete gastric vagotomies show that this hypersecretion is the factor that causes the ulcers and how it prevents them from healing, and that it is primarily, if not exclusively, of nervous origin. [4] Patients with duodenal and gastrojejunal ulcers frequently have hypertonicity and hypermotility of the stomach, which are also of neurological origin. While there is no doubt that these patients' epigastric discomfort is a result of their hypertonicity and hypermotility, they may be just one of the variables in the development of ulcers. [5]

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*Picrorhiza kurroa* is a well-known plant used in Ayurvedic medicines belonging to the family, Scrophul- ariaceae. This herb has been traditionally used in treating liver disorders, upper respiratory tract disorders, reduce fever, scorpion stings, and treat dyspepsia and chronic diarrhea. Picrorhiza kurroa (common name: Picrorhiza, katuka, kutki) is a small perennial herb growing in the hilly parts of the North-Western Himalayan region in India and Nepal. [7].

**Infection with Helicobacter pylori**

Helicobacter pylori stomach colonisation has been observed in people with peptic ulcer syndrome. Most often, H. pylori, a spiral-shaped microaerophilic gram-negative bacillus, causes chronic active gastritis (0.2 to 0.5 pm in length). The mucus gel layer that covers the stomach mucosa and the gap between it and the apical regions of the gastric mucosal epithelial cells constitute the two places where H. pylori is frequently discovered during gastric colonisation. Although it adheres to the luminal surfaces of gastric epithelial cells, Helicobacter pylori does not enter the gastric mucosa. [8].

## Material and Methods

The rhizome of Picrorbiza kurrooa were supplied by local vendor and it was identified from Indian Botanic Garden, Botanical Survey of India, Howrah, India.

**Collection of plant sample**

The fresh leaves and roots, rhizome of **PICRORHIZA KURROA** were collected. The plant was identified and authenticated by Ms. Mahima of Vedanta Testing and Research laboratory, Bhopal

**Organoleptic Characterization:**

Colour, odour, shape, test and size of the rhizomes and bark were observed

**Chemicals**

Chemicals like DNA, BSA, 2-thiobarbituric acid (TBA), 1,1',3,3'- tetramethoxypropane, 5,5'-dithiobis-2- nitrobenzoic acid (DTNB), ethylene diamine tetraacetic acid (EDTA), catalase and prostaglandin were purchased from Sigma Chemical Company, MO, St Louis, USA. Glutathione and epinephrine were purchased from S.d. fine-chemicals, Bombay, India. Other chemicals and solvents were of analytical grade and were mostly purchased from BDH and E-Merck.

**Animals**

For experimental study the animals used for different model were as follows:

1) Charles Foster strain rats (150-200 g body weight) of either sex.

2) Mice (weighing between 20-25 g).

All the animals were reared in the laboratory under uniform condition, maintaining controlled room temperature (26 ± 1°C) and light cycle (14 h light and 10 h dark) for at least 10 days and fed with pellet food (obtained from Hindustan Lever Ltd., India) and water ad libitum. The animals were housed in standard metal cages.

**Extraction**

The fresh plant rhizomes will be dried at 40±5° and crushed properly. One kilogram of powdered material will be extracted with ethanol:water (95:5, v/v) The ethanol solutions will be combined and dried in a rotatory evaporator at 40±5° (130 g). The crude ethanol extract (100 g) will be suspended in water and successively extracted with hexane (3×250 ml), chloroform (3×250 ml), ethyl acetate (3×250 ml), and n-butanol (3×250 ml) .[9].

**Confirmation of the extract the analytical methods**

HPLC analysis will be performed with a Waters HPLC system equipped with 600 quaternary gradient pumps, (7725i Rheodyne injector) Waters 717 plus autosampler, 996 PDA detector, and Empower 2 software (version-4.01). The temperature of the column will be set at 30±1°. Elution of standards and samples (20 µl) will be performed [8]. The mobile phase will be acetonitrile:water (10:90%, v/v). The flow rate will be 1 ml/min, the run time 20 min, and the detection wavelength will be set at 254 nm. Identification of compounds was performed on the basis of the retention time, s and spectral matching with standard. A series of standard solutions of picein were prepared to obtain solutions with final concentrations of 200, 100, 50, 25, 12.5, 6.25, 3.12, and 1.56 µg/ml. [10-12]

**Effect of Test Drugs (Fl, F2 and F3) at Different Doses on Gastric Cytoprotection**

Picrorhiza kurrooa rhizome extract has an extremely high concentration, with an LD50 of > 2.5 g/kg p.o. in mice. One advantage of knowing the LD5Q early in the development of a novel drug is that it can be used to calculate the doses

required to identify the drug's pharmacological activity spectrum. In an experiment, we used a range of doses, including 10, 15, 20, 50, and 100 mg/kg body weight, p.o. on a variety of experimentally created ulcer models in rats, to identify the protective dosage of the test drugs (F1, F2 ) based on the aforementioned report.

**Toxicity Studies**

An acute toxicity study is typically conducted on a novel drug or substance to identify the cause and severity of any adverse reactions observed in the central nervous system. Toxicological tests on the test material (F1, F2) were consequently carried out. The standard oral route was employed to evaluate the toxicity of the test drug[13]. Colony-bred Albino Swiss mice weighing 20–25 g were used during the experiments. Animals were provided full access to water and conventional pellet food (Hindustan Lever Ltd.) during the trial. Animals were not fed for the previous 17 hours prior to the experiment commencement. The test drugs' acute toxicity (F1, F2) was assessed in groups of six male mice. The dosages for the test medications were chosen to be 20 mg/kg body weight, which is 10 times more than the effective dosage of 20 mg/kg body weight. Five groups of mice and rats received the test treatments via oral administration. For three days straight, the mortality rates (% of mortality) and CNS effects in each group were recorded at 24-hour intervals. [14][15].

**Pylori ligation rat method-**

Pylorus ligation significantly increased stomach acid concentration compared to acute fistula rats without ligation. The gastric secretory pattern remains the same after ligating the pylorus and the stomach on the antrum. Cocaine, mecamylamine, and atropine were locally injected into the pylorus sac lumen to restrict gastric output. Mecamylamine was three times as efficient as and atropine was four times as potent locally as when administered orally, showing direct actions on submucosal nerve structures[16]. Since neither pylorectomy, duodenectomy, nor the injection of acid into the duodenum impact the acidity of the stomach, direct hormone release as a result of ligation did not appear to have played a significant part in the stimulation. Pylorus ligation did not promote flap secretion in rats with vagally denervated gastric pouches, further pointing to a nonhormonal mechanism. The stimulation of pressure receptors in the antral mucosa, which set off a vagovagal response, was thought to be the cause of the hypersecretion.. [17]

## Results and Discussion

**Macroscopy:**

**Color:** The rhizomes are deep grayish-brown in color,

externally white, blackish internally with whitish wood.

**Odor:** Slight and unpleasant.

**Taste:** Bitter.

**Size:** 3 to 5 cm in length and 0.5 to 1 cm in diameter.

**Shape:** Cylindrical pieces with longitudinal wrinkles and annulations at the tip.

**Features:** Conical, buds, and stems along with the roots also constitute the drug. The roots are longitudinally wrinkled with transverse cracks. Fracture is tough. The result was shown in **Fig. 1**.

**Microscopy:** The transverse cut of the root shows 20–25 layers of cork made up of cork cambium and cells with tangential extensions. Vascular bundles can be found in the cortex, which has many layers. A single layer of cells with strong walls surrounds the vascular bundles. A few dispersed fibres, 2-4 layered cambium, and phloem parenchyma make up the secondary phloem. Xylem fibres, tracheids, vessels, and parenchyma make up the secondary xylem. The tracheids are lengthy, lignified, have thick walls, and are roughly cylindrical. The xylem parenchyma has thin walls, is polygonal in shape, and has a tiny pith in its centre made up of thin-walled cells. It has a plain elliptical to oval form and contains starch granules.

**Extraction of Plant Materials**

It's worth noting that the ethanol extract (F2) of Picrorhiza kurrooa rhizome was discovered to be more powerful than the crude (F1)As a result, we

focused our further research on the ethanol extract (F2) of Picrorhiza kurrooa rhizome. The test medicine was crude powder, ethanol extract.

| Sr. No. | Retention Time | Area |
|---|---|---|
| 1 | 7.788 | 148752 |
| 2 | 7.926 | 247773 |
| 3 | 8.341 | 1563665 |
| 4 | 25.306 | 4066 |
| 5 | 37.628 | 79508 |
| 6 | 32.988 | 79361 |
| 7 | 34.580 | 119227 |
| 8 | 34.807 | 410508 |
| 9 | 35.061 | 151983 |
| 10 | 35.833 | 1273430 |
| 11 | 37.121 | 24480 |
| 12 | 37.626 | 79508 |
| 13 | 38.988 | 23508 |
| 14 | 42.180 | 12568 |
| 15 | 49.954 | 686266 |
| 16 | 50.666 | 889546 |
| 17 | 51.756 | 281617 |
| 18 | 52.707 | 183873 |

**Table 1: HPLC chromatogram of Alcohol:DCM/ 1:1 extract of P. kurroa showing the major identified 18 compound**

**Preparation of Drug from Different Extracts**

Weighing the dry material (various extracts) It was then ground in a mortar and pestle with a little amount of gum acacia (about 2%), then macerated in double distilled water. It is important to note that during our experiment it has been found that the ethanol extract (F2) of the rhizome of Picrorhiza kurrooa is more potent compared to the water extract (F2). Therefore we concentrated our further studies particularly on ethanol extract (F2) of the rhizome of Picrorhiza kurrooa. The crude powder, water extract and ethanol extract was used as test drug and gum acacia powder as vehicle.

**Confirmation of the extract the analytical methods**

For identification and confirmation, a qualitative HPLC analysis of an alcohol:DCM/ 1:1 extract of P. kurroa was performed. As a result, we gathered all of the markers and conducted further HPLC analysis. Figure 5 illustrates the HPLC chromatogram. 2 Other details about the retention time and area can be found in (Table no. 5.2)

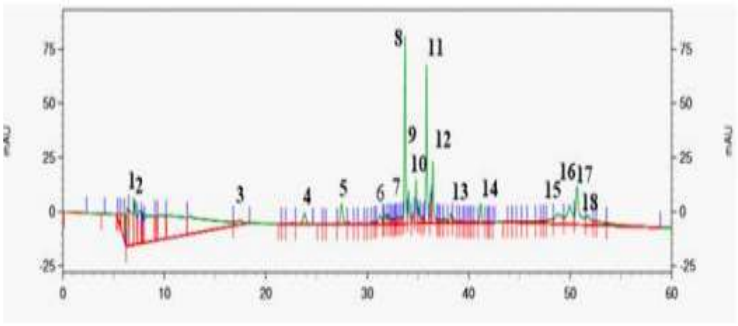


**Figure 6.1: HPLC chromatogram of Alcohol:DCM/ 1:1 extract of P. kurroa showing the major identified 18 compounds**

| S. NO | Phytochemical test | Inference |
|---|---|---|
| 1 | Carbohydrates | + |
| 2 | Flavonoids | + |
| 3 | Glycosides | - |
| 4 | Saponins | + |
| 5 | Aminoacids | + |
| 6 | Alkaloids | + |

**Phytochemical screening**:
The plant extract was subjected to the different phytochemical screening for the identification of the different phytochemical constituents.

**Experimental animals: T**he Wistar rats weighing about 150-180 gm were procured from the animal house. The animals were housed under standard well maintained 12:12 h dark and light cycle in a standard environment (Temp 23± 100 C) with relative humidity 50 ± 10 %. The animals were free to access to water and ad libitum with a standard rodent diet. The present study was approved by the institutional animal ethical committee (IAEC) bearing CPCSEA registration No-516/PO/C/01/IAEC.

**Pyloric ligation induced Gastric ulceration**: To study the effects of the test drugs (F1 , F2 ) on gastric secretion, the pyloric ligation of the stomach standardised in our laboratory was performed. The animals were divided in four groups, The control group was orally treated with gum acacia (2% solution). The test drugs (F1,F2) were administered orally for seven consecutive days at the different dose/ body weight. On the 8th day, the abdomen of the animals were opened under light ether anesthesia for pyloric ligation. After closure of the abdomen, the animals were put into cages under light restraint and allowed to recover from the anesthesia. The animals were sacrificed after 6 hours of pyloric ligation. The abdomen was opened and a ligature was placed around the esophagus. Stomach was removed and the contents were drained into a graduated centrifuge tube after making a small nick along the greater curvature adjacent to pyloric ligation. The gastric contents were collected, measured, centrifuged and subjected to biochemical analysis.

**Assessment of Cytoprotective Activity**

***Fig:2 without drug pretreatment***

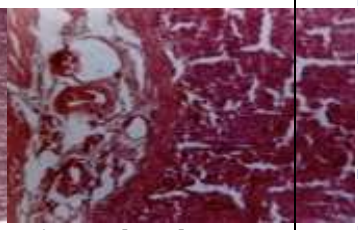

***Fig: 3 Ethanol extract pretreatment***

**Table: 3 Effect of Test Drugs (F1 F2 ) on Pyloric ligation Induced Ulcer**

| Treatment | 0 dose | 10 dose | 15 dose | 20 dose | 50 dose | 100 dose |
|---|---|---|---|---|---|---|
| Vehicle | 28.72 ± 1.4 | - | - | - | - | - |
| Water extract (F2) | - | 26.78 ± 0.38 | 25.17 ± 1.24 | 23.20 ± 1.21 | 22.60 ± 1.15 | 21.78 ± 1.07 |
| Ethanol extract (F3) | - | 19.37 ± 1.84 | 12.14 ± 1.09 | 4.35 ± 1.61 | 4.31 ± 1.24 | 4.80 ±0.89 |

**n = 6 rats in each group, Values are mean + SEM, Significant compared to vehicle-treated group, p <0.001**

All these findings thus suggest that treatment with the water extract (F1) and ethanol extract (F3) of the rhizome of Picrorhiza kurrooa at the dose of 20 mg/kg body weight significantly protects the gastric mucosa. There is no further increase in protection even with the higher doses. Therefore we have selected 20 mg/kg body weight as the treatment dose for our studies.

**Table 4. Effect of Test Drugs (F1 F2 ) on Acute Toxicity and Gross CNS Observations**

| Experimental drug powder | water (F1) | Ethanol (F2) |
|---|---|---|
| OBSERVATION | - | - |
| Gross Activity | - | - |
| Stimulation | - | - |
| Depression | + | + |
| Respiration | - | - |
| Ataxia | - | - |
| Tremor | - | - |
| Convulsion | - | - |
| (Clonic/Tonic) | - | - |
| Posture and Tone | - | - |

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| | | |
|---|---|---|
| Body | - | - |
| Tail (Strub) | - | - |
| Inclined Plane Test | - | - |
| Eyes | - | - |
| Pupil | - | - |
| Sound | - | - |
| Touch | - | - |
| Reflexes | - | - |
| Righting | - | - |
| Pilo-erection | - | - |
| Salivation | - | - |
| Lacrymation | - | - |
| After 24 hrs. | 100 | 100 |
| After 48 hrs. | 100 | 100 |

**- = absent, + = slight effect,**

**Histopathological Studies**

In the histological studies as shown in the **Figure,** the control group shows a diffuse mucosal ulceration, severe inflammatory cells infiltration in mucosa and sub-mucosa. There was a diffuse mucosal ulceration consisting of predominantly necrosis and acute inflammatory cells and some of the glands show necrosis. The group administered with Picrorhiza kurrooa crude drug dose of (20 mg/kg) shows gastric mucosa with intact epithelium, lamina propria and muscularis mucosa.

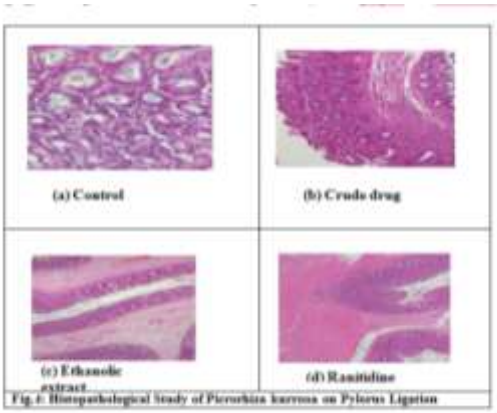

Fig. 4: Histopathological Study of Picrorhiza kurrooa on Pylorus Ligation

**Assessment of Antiulcer Property By Selected Extract Of Drug -**

**Pylorus Ligation Induced Gastric Ulcers**

The effects of drugs are shown in the Figure 3 &.4

**Table 5: The Effect of Extracted drug from Picrorhiza kurrooa on Ulcer Index, Ulcer Score, % Inhibition of Ulceration in Pylorous Ligation Model.**

| Group | Treatment | Dose (mg/kg b.w.) | Ulcer Score | Ulcer Index | %Inhibition of Ulceration |
|---|---|---|---|---|---|
| I | Control | 1 ml | 2.72±0.02 | 11.14±0.01 | 0 |
| II | ethanol extract of Picrorhiza kurrooa | 20 | 1.24±0.12** | 5.20±0.01** | 61.76*** |
| III | Ranitidine, a standard drug | 50 | 1.12±0.0*** | 5.12±0.00*** | 73.45*** |

**All the values are mean±SEM n=6. ***P<0.001, **P<0.01, compare vs. control, data was analysed using one way ANOVA followed by Tukey multiple comparison test**

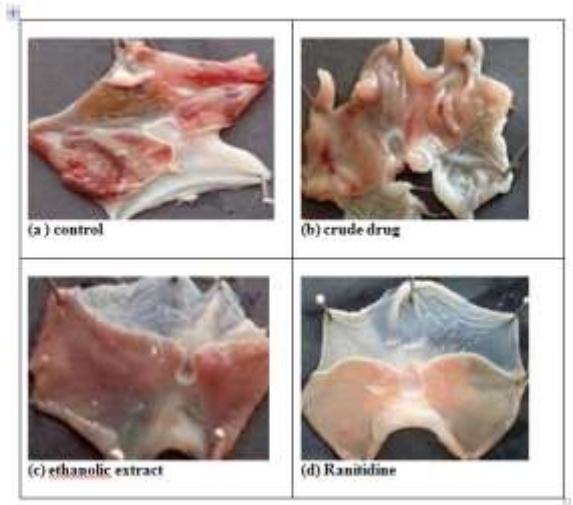

**Fig. 5: Effect of Picrorhiza kurrooa on Pyloric Ligated Rats**

**Therapeutic Effect of Ethanol Extract (F2)**

**Effect on Healing of Ulcer**

Ulcer induced by Pylorous Ligation healed in a progressive manner by oral administration of the ethanol extract of the rhizome of Picrorbiza kurrooa at a dose of 20 mg/kg body weight for 30 days compared to the untreated control group. The histological study also shows the normalisation of the ulcerated area after treatment with the ethanol extract for 30 days **.**DNA and protein content in total gastric mucosa also increases during the process of healing. The drug treated group healed at faster rate (96%) within 30 days whereas untreated ulcerated group till that time period recovered only 52% **(Table 6).**

**Table 6. DNA and Protein Content of Gastric Mucosa During the Process of Healing**

| Group | 0 Day | | 8th Day | | 15th Day | | 30th Day | |
|---|---|---|---|---|---|---|---|---|
| | DNA mg/g | Protein mg/g | DNA mg/g | PROTEIN mg/g | DNA mg/g | Protein mg/g | DNA mg/g | Protein mg/g |
| Group I control | 1.80 ±0.18 | 64.5± 2.25 | | | | | | |
| Group B Untreated ulcer | 0.71 ± 0.20 | 23.76 ±2.10 | 0.77 ±0.10 | 26.21 ±1.48 | 0.82± 0.086 | 27.4± 1.85 | 0.92± 0.17 | 32.4± 2.30 |
| Group III | | | 0.97 ±0.11 | 33.05 ±2.70 | 1.78± 0.10 | 56.34 ±2.78 | 1.81± 0.02* | 60.47 ±2.48 * |

n = 6 rats in each group, ‘2 rats expired during the experiment, ^Significant compared to untreated ulcerated group, $p < 0.001$

**Effect of Ethanol Extract (F2) on Histamine Content**

Treatment with the ethanol extract (F2) for 15 consecutive days (20 mg/kg body weight), significantly decreases the level of histamine in gastric tissue compared to the ulcerated group (0 day as well as 15 days) of rats **(Table 7).**

**Table 7. Effect of Ethanol Extract (F2) on Histamine Content in Gastric Mucosa**

| Group | Histamine content pg/mg of protein ± SEM |
|---|---|
| **Control** | 0.558 ± 0.032 |
| **Ulcerated (0 day)** | 0.645 ± 0.052 |
| **After 15 days (ulcerated) without treatment** | 1.07 ± 0.026b |
| **Treatment with ethanol extract (F3)** | 0.546 ±0.056*a |

n = 10 rats in each group, ^Significant compared to the ulcerated group (0 day), $p < 0.05$, Significant compared to the ulcerated group (15 days), $p < 0.001$, ^Significant compared to the control, $p < 0.001$

## Conclusion

The present study, based on the rhizome of the plant Picrorhiza kurrooa, evaluates the effect of the water extract (F1) and ethanol extract (F2) on gastric cytoprotection as well as its therapeutic benefits with possible mechanisms involved. The findings of this study make it clear that preliminary treatment with the test drugs (F1, F2) at a dose of 20 mg/kg body weight significantly inhibits/reduces the development of an experimental acute ulcer in the rat's stomach (Table 5) and provides protection to the extent of almost 60% and 85% after seven days of treatment with F1 and F2, respectively.These results strongly show that the rhizome portion of the plant Picrorhiza kurrooa, both the water soluble (F1) and the ethanol soluble fraction (F2), has cytoprotective properties for the stomach. In general, the majority of flavonoids and polyphenols are found in ethanol extract (F2). Many of these F2 component parts have antioxidant properties. Our future objective is to do a thorough analysis on the isolation of active components.

In our experimental study, the histopathological results (Figure 4) clearly show that oral administration of an ethanol extract (F2) of the

Picrorhiza kurrooa rhizome to ulcerated rats almost completely reverses the gastric mucosal lesions caused by indomethacin within 30 days, whereas the ulcerated rats left untreated only experience a 52% recovery. Thus, F2 therapy promotes up the healing process; According to all of the studies mentioned above, Picrorhiza kurrooa rhizome water extract (F1) and ethanol extract (F2) at a dose of 20 mg/kg body weight significantly protects the stomach wall against different experimentally generated gastric ulcers in various ways. Since it is known that tissue injury is always accompanied by a loss or reduction in DNA content and a reduction in protein synthesis, we looked at the DNA and protein content of the stomach mucosal tissue as the ulcer was healing in order to evaluate how well the wound was mending. Since all diploid cells from the same animal should have a similar amount of DNA, a biochemical analysis of the tissue's DNA content can be used to determine how many cells are present overall in the tissue. According to the experimental results (Table 6), when treated with an ethanol extract (F2) of the Picrorhiza kurrooa rhizome, mucosal restitution occurs more quickly than in the ulcerated group that was not treated. Similar findings were made by Myszor et al., who found that the main reason for the lower proliferation was a delay in the gastric mucosal epithelium's process of cell renewal. It is clearly apparent from the results that the ulcer group's lower cell count was caused by the development of mucosal ulcers, which led to the loss of epithelial cells. These findings clearly show the test medicine (F2)'s cumulative impact on gastric ulcers, demonstrating the effectiveness of its antiulcerogenic properties.

These findings lead to the conclusion that the test drug (F2)'s antiulcerogenic activity may originate from a change in the biotransformation of the toxic substances, which lowers the production of reactive metabolites. All of these results suggest that the test medications (F1 and F2) made from the rhizome of Picrorbiza kurrooa prevent stomach ulcers in a variety of ways, depending of the causes. To determine the therapeutic potential and safety of these test medications in the treatment of peptic ulcer disease, however, more comprehensive studies on various acute and chronic models of ulceration are required.

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