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Evaluation of antiulcer activity on roots of *Picrorhiza kurroa* by usingPyloric ligation rat models

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Abstract

In order to confirm the chemical contents of *Picrorhiza kurooa* rhizome extract, HPLC was used to analyse the rhizome. The capacity to give stomach protection was investigated at various dosages of 1, 5, 10, 20, and 50 mg/kg determined based on the acute toxicity research in Wister rats, which were used in this investigation. Several metrics, such as stomach volume, pH, total acidity, free acidity, ulcer index, and percentage inhibition of ulceration, were used to gauge the degree of gastric protection. The medicine of choice 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.

Keywords: Picrorhiza kurroea, peptic ulcer, pylorus ligation, ulcer index, gastric protection

Introduction

Ulcer a disease condition, occurs as a result of an imbalance between the aggressive factors (acid and pepsin) and mucosal defense factors (mucous, bicarbonate, and prostaglandins) due to oxidative stress. The pathophysiology of ulcer suggest that ulcer is mostly caused by the bacteria Helicobacter pylori and persistent use of non-steroidal anti-inflammatory drugs (NSAIDs) [1]. The acteria and NSAIDs cause ulcers by damaging the mucus of the stomach lining through mechanism of inflammation, thereby exposing the interior of the stomach to acid which irritates the tissue and causes peptic lesion in the stomach [2-3]. An excessive secretion of gastric juice, both in the fasting stomach and in response to the ingestion of food, has been found to be presentin most, if not all, patients with duodenal and gastrojejunal ulcers, when appropriate methods for its detection have been employed.

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Observations on patients with peptic ulcer who have been treated by complete gastric vagotomy, supported and amplified by studies on experimental animals, indicate that this hypersecretion is the cause of the ulcers, is the chief factor which prevents them from healing, and that it is predominantly, if not exclusively, of nervous origin.

[4] Hypertonicity and hypermotility of the stomach are likewise usually present in patients with duodenal and gastrojejunal ulcers, and are also of nervous origin. While there is no doubt that this hypertonicity and hypermotility contribute to the epigastric discomfort of these patients, theyare probably of minor importance in the cause of ulcer. [5]

Infection with Helicobacter pylori

Helicobacter pylori colonisation of the stomach has been described in patients with peptic ulcer syndrome. H. pylori is a spiral-shaped microaerophilic gram-negative bacillus that typically causes chronic active gastritis (0.2 to 0.5 pm in length)[71]. H. pylori is typically located in the deep sections of the mucus gel layer that covers the gastric mucosa and between the mucus gel layer and the apical surfaces of gastric mucosal epithelial cells during gastric colonisation. Although Helicobacter pylori adheres to the luminal surfaces of gastric epithelial cells, it does not enter the gastric mucosa[6].

Material and Method

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

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. Glutathioneand 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: Charles Foster strain rats (150-200 g body weight) of either sex. 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 root will be dried at 40±5° and crushed properly. One kilogram of powdered material will be extracted with ethanol:water (95:5, v/v) (1×7 l, 1×3.5 l, 6×1 l). The ethanol solutions will be combined and dried in a rota 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) and evaporation of the solvents at reduced pressure gave 6.6 g of *n*-hexane g of chloroform, 1.5 g of ethyl acetate and 23.2 g of *n*-butanol extract [7].

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. [9-12]

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

LD50 of Picrorhiza kurrooa rhizome extract was reported77 to be > 2.5 g/kg p.o. in mouse, which is a rather high concentration. A benefit of knowing the LD5Q early in the development of a novel medicine is that the doses needed to determine the drug's pharmacological activity spectrum may be deduced from the fatal dosage. On the basis of the aforementioned report, we conducted an experiment to determine the protective dosage of the test medications (Fp F2 and F3), for which we used a range of doses, namely 10, 15, 20, 50, and 100 mg/kg body weight, p.o. on a variety of experimentally generated ulcer models in rats.

Toxicity Studies

It is normal for a novel medicine or substance to undergo an acute toxicity study to determine the origin and degree of any adverse response seen in the central nervous system. As a result, toxicological investigations on the test substance (F1, F2, and F3) were conducted. To assess the test drug's toxicity, a standard oral route was used[13]. We utilised Albino Swiss mice that were colony bred and weighed between 20-25 g. Prior to the trial, animals were given unrestricted access to conventional pellet food (Hindustan Lever Ltd.) and water. Animals were not fed for the previous 17 hours prior to the experiment's commencement. In groups of six male mice, the acute toxicity of the test medicines (Fj, F2, and F3) was determined. The doses of the test edications were chosen to be 20mg/kg body weight, which is ten times the highest effective dosage, which is 20 mg/kg body weight. Oral administration of the test medications was used to administer the drugs to five groups of mice and rats. Simultaneously, the mortality rates percentage of deaths) and CNS effects in each group were documented at 24-hour intervals for three consecutive days[14][15].

Pylori ligation rat method-

Pylorus ligation significantly increased gastric acid concentration over that found in nonligated acute fistula rats. Ligating the stomach on the antrum did not change the gastric secretory pattern from that obtained by pylorus ligation. Local administration of atropine, mecamylamine, and cocaine into the lumen of a pylorus sac inhibited gastric secretion. Atropine was four times as potent and mecamylamine three times as potent locally as when given orally, indicating direct effects on nerve structures in the submucosa[16]. Direct hormonal release as a result of ligation did not appear to have a major role in the stimulation, since neither pylorectomy, duodenectomy, nor the infusion of acid into the duodenum reduced gastric acidity. Pylorus ligation in rats wIth vagally denervated gastric pouches did not stimulate pouch secretion, also suggesting a nonhormonal mechanism. The hypersecretion was postulated to be due to stimulation of pressure receptors in the antral mucosa which initiated a vagovagal reflex. [17]

Result and Discussion

Extraction of Plant Materials

It's worth noting that the ethanol extract (F3) of Picrorhiza kurrooa rhizome was discovered to be more powerful than the crude (F1) and water extracts during our experiment (F2). As a result, we focused our further research on the ethanol extract (F3) of Picrorhiza kurrooa rhizome. The test medicine was crude powder, water extract, and ethanol extract, with gum acacia powder serving as the carrier.

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 was transferred into a tiny tube and the volume was adjusted as needed for several experiments. Before administration, the medication suspensions were newly produced.

Confirmation of the extract the analytical methodsInfrared spectra of P. kurroa

DCM infrared spectra (IR): The presence of various peaks with regard to their frequency in a methanol (1:1 v/v) extract of P. kurroa indicates that the extract contains diverse biomolecules. Those compounds have functional groups such as OH, COO, CN, and COO-CO, as shown by the wave numbers in (Table no. 1) & (Table no. 2). (Fig. no.1)

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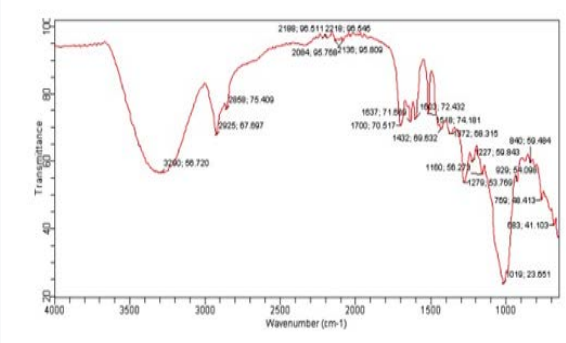

Table 1 : IR spectra data of P. kurroa

Sr. No.	Wave number	functional group
1.	3290.56.720	O-H stretching alcohol
2.	2925.67.697	alkane
3.	2858:75.409	C-H stretching alkane
4.	1750.70.517	Esters, delta lactone
5.	1637:71.669	C=C stretching, alkene, conjugated alkene, amine, cyclic amine
6.	1603:72.432	C=C stretching, N-H bending, cyclic alkene, amine,conjugated alkene
7.	1019:23.651	C-H streching

Qualitative phytochemical profiling of Alcohol:DCM/ 1:1 extract of P. kurroa by HPLC

For identification and confirmation, a qualitative HPLC analysis of an alcohol:DCM/ 1:1 extractof 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)

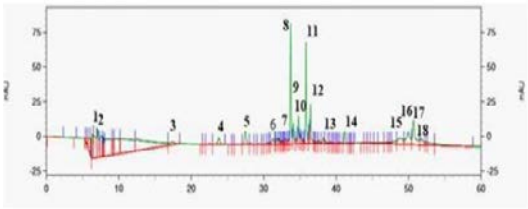

Figure 2: HPLC chromatogram of Alcohol:DCM/ 1:1 extract of P. kurroa showing the major identified 18 compounds

Sr. No.	Retention Time	Area	Percentage of to area
1	7.787	148751	0.65
2	7.927	247774	1.09
3	8.340	1563666	6.85
4	25.307	4065	0.02
5	37.627	79507	0.35
6	32.987	79360	0.35
7	34.580	119227	0.52
8	34.807	410509	1.80
9	35.060	151984	0.67
10	35.833	1273431	5.58
11	37.120	24480	0.11
12	37.627	79507	0.35
13	38.987	23509	0.10
14	42.180	12569	0.06
15	49.953	686267	3.01
16	50.667	889545	3.90
17	51.753	281618	1.23
18	52.707	183873	0.81

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

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

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Experimental animals: The 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 and F3) 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 and F3) 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. 3 Without Drug Pretreatment (Magnification 100 X)

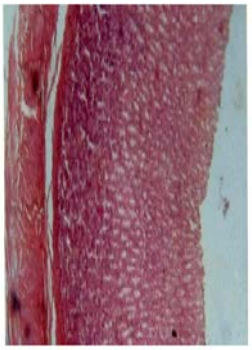

Fig.4 Ethanol Extract (F3) Pretreated (Magnification 100 X)

Table 2 : Effect of Test Drugs (F1 F2 and F3) on Pyloric ligation Induced Ulcer

Treatment	0 dose	10 dose	15 dose	20 dose	50 dose	100 dose
Vehicle	28.72	-	-	-	-	-
Crude powder (F,)	-	21.53	14.70	9.78	9.40	8.90 ± 0.4
Water extract (F2)	-	26.78	25.17	23.20	22.60	21.78
Ethanol extract (F3)	-	19.37	12.14	4.35	4.31	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 crude powder (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 3. Effect of Test Drugs (F1 F2 and F3) on Acute Toxicity and Gross CNS Observations

Experimental drug powder	Crude (F1)	Water (F2)	Ethanol (F3)
Observation	-	-	-
Gross Activity	-	-	-
Stimulation	-	-	-
Depression	+	+	+
Respiration	-	-	-
Ataxia	-	-	-

Tremor	-	-	-
Convulsion	-	-	-
(Clonic/Tonic)	-	-	-
Posture and Tone	-	-	-
Body	-	-	-
Limbs	-	-	-
Tail (Strub)	-	-	-
Cataleps	-	-	-
Inclined Plane Test	-	-	-
Eyes	-	-	-
Pupil	-	-	-
Ptosis	-	-	-
Reaction to	-	-	-
Sound	-	-	-
Touch	-	-	-
Reflexes	-	-	-
Pinnial	-	-	-
Righting	-	-	-
Pilo-erection	-	-	-
Cyanosis	-	-	-
Salivation	-	-	-
Lacrymation	-	-	-
After 24 hrs.	100	100	100
After 48 hrs.	100	100	100
After 72 hrs.	100	100	100

- = absent, + = slight effect,

Assesment Of Antiulcer Property By Selected Extract Of Drug –

Pylorus Ligation Induced Gastric Ulcers

The effects of drugs are shown in the Figure 8.3 &8.4

Table 4: The Effect of Extracted drug from Picrorhiza kurrooa on Ulcer Index, Ulcer Score, % Inhibition of Ulceration in Pylorous Ligation Model

Group	Treatment	Dose	Ulcer Score	Ulcer Index	%Inhibition
I	Control	1 ml	2.71±0.02	11.15±0.01	0
II	crude powder	20	1.71±0.25**	6.30±0.013**	34.62**
III	ethanol extract	20	1.23±0.12**	5.22±0.01**	60.76***
IV	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

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(a) Control

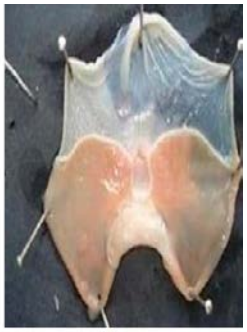
Fig: 4

(b) crude drug

Fig: 5

(c) ethanolic extract drug

Fig: 6



(d). Ranitidine

Fig: 7

Table 5: The Effect of Extracted drug from Picrorhiza kurrooa on Pepsin Content, Total Protein Content and Mean Mucin in Pylorous Ligation Model

Group	Treatment	Dose (mg/kg b.w.)	**Pepsin Content**	**total Protein Content**	**Mean Mucin**
I	Control	1 ml	38.83±6.23	18.33±2.21*** 7	0.08±0.011
II	crude powder	20	22.83±4.43**	75.85±5.13**	0.14±0.021***
III	ethanol extract	20	19.83±2.42***	71.85±4.15***	0.15±0.062***
IV	Ranitidine, a standard drug	50	18.33±2.21*** 7	70.85±3.63***	0.12±0.065***

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.

Therapeutic Effect of Ethanol Extract (F3) 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 **(Figure).** 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 . DNA and Protein Content of Gastric Mucosa During the Process of Healing

Group	0 Day		7th Day3		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

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Group I control	1.82 ±0.18	62.4 ±2.25						
Group B Untreated ulcer	0.72 ± 0.20	23.76± 2.13	0.78 ±0.10	25.21± 1.48	0.82 ±0.086	27.4 ±1.85	0.93 ±0.17	32.4 ±2.30
Group III			0.95 ±0.11	33.05± 2.70	1.78 ±0.12	56.35± 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 (F3) on Histamine Content

Treatment with the ethanol extract (F3) 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. Effect of Ethanol Extract (F3) on Histamine Content in Gastric Mucos*a*

Group	Histamine content pg/mg of protein ± SEM
Control	0.559 ± 0.032
Ulcerated (0 day)	0.645 ± 0.050
After 15 days (ulcerated) without treatment	1.08 ± 0.026b
Treatment with ethanol extract (F3)	0.545 ±0.055*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

Table 8: The Effect of Ethanolic Extract of Sesamum indicum on Ulcer Index, Ulcer Score, *% Inhibition of Ulceration in Pylorous Ligation Model*

Group	Treatment	Dose (mg/kg b.w.)	Ulcer Score	Ulcer Index	%Inhibition
I	Control	1 ml	2.71±0.02	11.15±0.01	0
II	crude powder	20	1.71±0.25**	6.30±0.013**	34.62**
III	ethanol extract	20	1.23±0.12**	5.22±0.01**	60.76***
IV	Ranitidine,	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.

Conclusion

The present study with the rhizome part of the plant Picrorbiza kurrooa, evaluates the effect of the crude powder (F^, water extract (F2) and ethanol extract (F3) on gastric cytoprotection as well as its therapeutic uses with the plausible mechanism involved. It is evident from the results of the present investigation that pretreatment with the test drugs (Fj, F2 and F3) at the dose of 20 mg/kg body weight, significantly inhibit/reduce the development of a experimental acute ulcers induced in the rat's stomach (**Table 8.4)** and protection to the extent of almost 60% and 85% on seven days treatment with Fj and F3 respectively.

These results strongly suggest that both crude powder (F1) and ethanol soluble fraction (F3) of rhizome part of the plant Picrorbiza kurrooa possesses a gastric cytoprotective activity. Most of the flavonoids and polyphenol are usually present in ethanol extract (F3). Many of these component present in F3 also possess antioxidant property. However, a detailed study concerning the isolation of active components) is our future plan of work.

It was observed in our acute toxicity study that even at the higher tolerable dose in case of mice and rats, there was no death and the test drugs are devoid of any acute toxicity **(Table 8.5).** In this experiment slight depression for a short period was observed at the higher dose, i.e., 200 mg/kg body weight in mice and rat orally. The depression was not definitely contributed by CNS effect as there was none of its sign or symptoms in those groups, specially reaction to sound. and touch was absolutely normal. The depression was likely due to overdose of drug into the stomach after long fasting and soon it disappeared as the drug passes to the lower intestinal part. Maximal protection was observed with very small dose (20 mg/kg body weight) of the test drug indicating that it has a higher safety margin.

The cytoprotective effect of this test drug may be explained in a number of ways of which gastric secretion study is an important one. Pretreatment with F1 and F3 increases the gastric mucosal barrier by increasing the gastric secretion of mucus **(Table 8.8)** when compared to the control, while acid output and pepsin content does not show any remarkable change **(Table 7 & 8).**

Prostaglandins form a vital component of gastric mucosal defense. They are found throughout the gut in high concentrations locally, and the major stimulus for their synthesis is cell trauma by acid or alkali. It has been also reported that a variety of prostaglandins particularly those of the E-series are potent inhibitors of basal and stimulated acid secretion. Prostaglandins may act directly on the parietal cells reducing both the intracellular synthesis of cyclic AMP as well as their own secretory activity. Endogenous prostaglandins (PGs) stimulate secretion of gastric mucus and gastric and duodenal bicarbonate. They participate in the maintenance of gastric mucosal blood flow and of the integrity of gastric mucosal barrier and promote epithelial cell renewal in response to injury. Prostaglandin E2 is also believed to increase the surface hydrophobicity of gastric mucosa by increasing surface-active phospholipid surfactant123. Ferdi et al85 have also reported that apocynin, a. drug isolated from the roots of Picrorhiza kurrooa, potentially enhanced the formation of the antiinflammatory PGEr Thus, the enhanced level of prostaglandin (PGE2) protect the stomach wall from NSAID induced gastric lesion may be attributed to any of the above mentioned pathways.

In our experimental therapeutic study the histopathological findings **(Figure 6)**, clearly indicates that oral administration of ethanol extract (F3) of the rhizome of Picrorhiza kurrooa to the ulcerated rats almost recover 96% within 30 days from gastric mucosal lesions caused by indomethacin whereas the untreated ulcerated rats recover only 52%. Treatment with F3 thus accelerates the rate of healing;

All the above mentioned findings thus suggest that crude powder (F1) and ethanol extract (F3) of the rhizome of Picrorhiza kurrooa at the dose of 20 mg/kg body weight significantly protects the stomach wall from different experimentally induced gastric lesions in a multiple ways.

It is established that tissue damage is always associated with the loss or reduction of DNA content and impairment of protein synthesis so we determined the DNA and protein content of the gastric mucosal tissue during the process of

healing as an index of ulcer healing. The DNA content is theoretically similar in all diploid cells of the same animal and therefore biochemical determination of the DNA content of the tissue provides an estimate of the total number of cells in the tissue. The experimental findings **(Table 9)** reveal that in mucosal restitution, epithelial integrity and continuity are rapidly reestablished on treatment with ethanol extract (F3) of the rhizome of Picrorhiza kurrooa compared to untreated ulcerated group. A similar observation has been reported by Myszor et alm, where a delay in the process of cell renewal in the gastric mucosal epithelium served as the principal cause of the decreased proliferation. From the results obtained, it is distinctively evident that the number of cells decreased in the ulcer group owing to the formation of mucosal lesions resulting in the loss of epithelial cells. These observations clearly indicate the cumulative effect of the test drug (F3) on gastric ulcer thereby providing evidence for its antiulcerogenic efficacy.

It is **concluded** from these results that the antiulcerogenic action of the test drug (F3) may be dueto an alteration in the biotransformation of the toxic substances resulting in decreased formation of reactive metabolites. All these findings suggest that the test drugs (Fj and F3), prepared from the rhizome of Picrorbiza kurrooa, protect the stomach from ulceration irrespective of the causal factors in a. number of ways. However, further indepth studies on different acute and chronic models of ulceration are necessary to establish the therapeutic potential and safety of these test drugs in the treatment of peptic ulcer disease.

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