EFFECTS OF PLUMERIA OBTUSA LINN. IN PEPTIC ULCER INDUCED BY PYLORUS LIGATION & INDOMETHACIN

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ABSTRACT

Peptic ulcer disease refers to pathological lesions and ulcers of any portion of gastrointestinal tract exposed to acid activated pepsin. Gastric ulcer refers to ulcer in the stomach where as duodenal ulcer is a ulcer found in duodenum of small intestine. Helicobacter pylori infection, a spiral shaped type of bacteria, is present in more than 90% of the patients with intestinal ulcers and more than 80% of patients with stomach ulcers. Helicobacter pylori weaken the protective mucus coating of the stomach and duodenum which allows acid to get through to the sensitive lining beneath. Both the acid and the bacteria irritate the lining and cause a sore, or ulcer. Long term use of anti inflammatory drugs (NSAIDs) or pain relievers such as aspirin, ibuprofen, and naproxen sodium. NSAIDs lower the stomach's resistance to the harmful effects of acid. Effects of Plumeria obtusa linn. was observed in peptic ulcer induced by pylorus ligation & indomethacin.

KEYWORDS: Peptic ulcer, plumeria obtusa Linn., pylorus ligation, indomethacin.

INTRODUCTION

The concept of ethnopharmacology has evolved from the requirement for studies in light of modern science on the drugs used in the traditional medicine. In 1981, Bruhn and Holmstedt defined ethnopharmacology as the interdisciplinary scientific exploration of biologically active agents traditionally observed by man. "In its entirety, pharmacology embraces the knowledge of the history, source, chemical and physical properties, compounding, biochemical and physiological effects, mechanism of action, absorption, distribution, biotransformation, excretion and therapeutic and other uses of drugs". An ulcer is a local defect, or excretion of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue. Peptic ulcer disease refers to pathological lesions and ulcers of any portion of gastrointestinal tract exposed to acid activated pepsin. Gastric ulcer refers to ulcer in the stomach whereas duodenal ulcer is a ulcer found in duodenum of small intestine. In the United States, PUD affects approximately 4.5 million people annually. Approximately 10% of the US population has evidence of a duodenal ulcer at some time. Of those infected with H pylori, the lifetime prevalence is approximately 20%. Only about 10% of young persons have H pylori infection; the proportion of people with the infection increases steadily with age.

MATERIALS AND METHODS

Collection of Plants

The bark was collected from, the campus of Barkatullah University Bhopal (M.P), in the month of August-September 2010. Barks were separated and were made completely clean and dust free.

Authentication of Plant

The plant was authenticated by Prof. Shaukat Shaheed Khan (Prof. of botany), Department of microbiology, Saifiya college, Bhopal (M.P.) and a specimen voucher no. APS-11 was assigned.

Preparation of Extraction

Plant material was separated into it component parts on receipt and dried. The dried, ground material was extracted with MeOH a Soxhlet apparatus for 8 hr. In the ratio of 1:5. Thereafter, the resulting methanol extract was reduced in vacuo (40 ºC), freeze dried and stored at 4 ºC until used. The yield was 11.69% (w/w).

Screening of Crude Extracts (Qualitative Phytochemical Analysis)

The extracts of Plumeria obtusa were subjected to qualitative analysis for the various phytocomstituents like alkaloids, carbohydrates, glycosides, phytoesters, saponins, tannins, proteins, amino acids and flavonoids.

Test for Alkaloids

- Hager’s test – Extracts treated with Hager’s reagent (Saturated picric acid solution), formation of yellow precipitate indicates the presences of alkaloids.
- Mayer’s test – Extracts treated with Mayer’s reagent (Potassium mercuric iodide solution) formation of cream precipitate indicates the presences of alkaloids.
- Dragendorff’s test – Extracts treated with Dragendorff’s reagent (Potassium bismuth iodide solution), formation of orange brown precipitate indicates the presences of alkaloids.
- Wagner’s test – Extracts treated with Wagner’s reagent (Iodine-potassium solution), reddish brown precipitate indicates the presences of alkaloids.

Test for Carbohydrates

- Molisch’s test<- Extract treated with Molisch reagent (α-naphthol in 95% ethanol) and few drops of concentrated H2SO4 were added at the sides of the test tube, violet ring appears at the junction indicates the presences of carbohydrates.
- Fehling’s test- Small portion of the extract treated with Fehling’s reagent (Fehling’s reagent A- Copper sulphate in water and Fehling’s reagent B- Sodium potassium tartarate), the mixture was heated; brick red color precipitate indicates the presences of reducing sugars.
- Barfoed’s test – Extracts treated with Barfoed’s reagent (Copper acetate in water and glacial acetic acid), the mixture was heated on a water bath, red color precipitate indicates the presences of sugars.
- Benedict’s test – Extracts treated with Benedict reagent (Copper sulphate, sodium Citrate and sodium carbonate in water), the mixture was heated on water bath for 10
minutes, red color precipitate indicates the presence of sugars.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Phytoconstituents</th>
<th>Methanolic extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbohydrates</td>
<td>+ve</td>
</tr>
<tr>
<td>2</td>
<td>Proteins</td>
<td>+ve</td>
</tr>
<tr>
<td>3</td>
<td>Flavonoids</td>
<td>+ve</td>
</tr>
<tr>
<td>4</td>
<td>Alkaloids</td>
<td>+ve</td>
</tr>
<tr>
<td>5</td>
<td>Glycosides</td>
<td>+ve</td>
</tr>
<tr>
<td>6</td>
<td>Saponins</td>
<td>+ve</td>
</tr>
<tr>
<td>7</td>
<td>Tannins</td>
<td>+ve</td>
</tr>
<tr>
<td>8</td>
<td>Triterpenoids</td>
<td>+ve</td>
</tr>
</tbody>
</table>

Table 1: Phytochemical Analysis

Test for Steroids, Triterpenoids and Cardiac glycosides

- **Liebermann-Burchard test**
  Small portion of the extracts were dissolved in 1ml of chloroform, to this 1ml acetyl chloride was added followed by addition of 2ml of concentrated sulphuric acid from the sides of the test tube. Formation of reddish violet color at the junction indicates the presence of steroids, triterpenoids and cardiac glycosides.

- **Salkowski test** – when few drops of concentrated sulphuric acid was added to the test solution in chloroform shaken and allowed to stand for few minutes formation of red color in the chloroform layer suggests the presence of steroids.

- **Bailjet test** – 1 ml of extract solution was treated with few drops of sodium picate reagent. Formation of yellowish orange color indicates the presence of cardiac glycosides.

- **Keller Killani’s test** – 5mg of extract was treated with 1ml of glacial acetic acid and few drops of ferric chloride solution were added in to the test tube. To this mixture 2 ml of concentrated sulphuric acid was added carefully along the sides of the test tubes. The formation of a reddish brown color at the junction of two layers and formation of bluish green upper layer indicates the presence of deoxy-sugar in the carbohydrates.

Test for Saponins

- **Froth test**- Diluted 1ml of the extract with distilled water to 20 ml and shaken in a graduated cylinder for 15min. One-centimeter layer of foam indicates the presence of saponins.

Test for Tannins

- **Ferric chloride test** – Extracts treated with ferric chloride solution, blue colour indicates the presence of tannins.

- **Lead acetate test** – Extracts treated with lead acetate solution, yellow precipitate indicates the presence of tannins.

Test For Proteins and Amino Acids

- **Millon’s test** – Extract treated with Millon’s reagent (Mercuric nitrate in nitric acid), red colour indicates the presence of proteins.

- **Biuret test** – Extract treated with sodium hydroxide and copper sulphate solution added drop wise and mixed, violet colour indicates the presence of proteins.

- **Ninhydrin test** – Extract treated with Ninhydrin reagent and ammonia, heated, violet colour indicates the presence of amino acids.

Test for Flavonoids

- **Ferric chloride test** – Extracts treated with few drops of neutral ferric chloride solution was added, blackish red colour indicates the presence of flavonoids.

- **Lead acetate test** – Extracts treated with lead acetate solution, yellow precipitate, indicates the presence of flavonoids.

- **NaOH & HCl test** – Extracts treated with dil NaOH and followed by addition of dil. HCl. A yellow solution give with NaOH, which turns colourless with dil. HCl confirms flavonoids.

Preparation of Formulation

After preparation of extract the next step was to formulate a extract of *Plumeria obtusa* which was then subjected to animal studies. 1 gm of *Plumeria obtusa* extract dissolved in 25 ml water.

Experimental Animals

Selection of Animal

Healthy Wistar rats of either sex weighing 170-200g were used for the study and housed individually under standard condition of temperature (25 ± 1°C ), 12 hr light/dark cycle and feed with standard pellet diet and water ad Libitum. The study was permitted by the Institutional animal ethical committee of Truba Institute of pharmacy, Bhopal (M.P.) with ethical clearance reference number TIP/IAEC/2011/PN-01.

The animal care was taken as per the guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Govt. of India.

Drug and Chemicals

Methanol, Pantoprazole, Dragendorff’s reagent (Potassium bismuth iodide solution), Mayer’s reagent (Potassium mercuric iodide solution), Sodium nitroprusside, Sodium picrate, Sulphuric acid, α-napthol, Chloroform, Acetic anhydride, Sodium hydroxide, CuSO₄, Sodium carbonate, Ferric chloride, Hydrochloric acid, Acetone, Oxalic acid, Toppers reagent (dimethylaminobenzene) and Phenolphthalein solution

Vehicles

Methanol and Distil water

LABORATORY MODELS FOR ANTI - ULCER ACTIVITY

- Pylorus ligation in rats (SHAY rat)
- Stress ulcer through immobilization stress
- Stress ulcers by cold water immersion
- Indomethacin induced ulcers in rats
- Ethanol induced mucosal damage in rats (cytoprotective activity)
- Subacute gastric ulcer in rats
- Gastric ischemia-reperfusion injury in rats

Pylorus Ligation in Rats (SHAY rat)

Procedure

Wistar rats weighing 150–170 g are starved for 48 h having access to drinking water ad libitum. During this time they are housed single in cages with raised bottoms of wide wire mesh in order to avoid cannibalism and coprophagy. Six animals are used per dose and as controls. Under ether anesthesia a midline abdominal incision is made. The pylorus is ligated, care being exercised that neither damage to the blood supply nor traction on the pylorus occurs. Grasping the stomach with instruments is to be meticulously avoided; else ulceration will invariably develop at such points. The abdominal wall is closed by sutures. The test compounds are given either orally
by gavage or injected subcutaneously. The animals are placed for 19 h in plastic cylinders with an inner diameter of 45 mm being closed on both ends by wire mesh. Afterwards, the animals are sacrificed in CO2 anesthesia. The abdomen is opened and a ligature is placed around the esophagus close to the diaphragm. The stomach is removed, and the contents are drained in a centrifuge tube. Along the greater curvature the stomach is opened and pinned on a cork plate. The mucosa is examined with a stereomicro-scope. In the rat, the upper two fifths of the stomach form the rumen with squamous epithelium and possess little protective mechanisms against the corrosive action of gastric juice. Below a limiting ridge, in the glandular portion of the stomach, the protective mechanisms are better in the mucosa of the medium two fifths of the stomach than in the lowest part, forming the antrum. Therefore, lesions occur mainly in the rumen and in the antrum. The number of ulcers is noted and the severity recorded with the following scores:

- 0 = no of ulcer
- 1 = superficial ulcers
- 2 = deep ulcers
- 3 = perforation.

Mean ulcer score for each animal will be expressed as ulcer index -

\[ U = U_N + U_S + U_F \times 10^2 \]

Where,

- \( U_N \) = average of number of ulcers per animal
- \( U_S \) = average of severity of score
- \( U_F \) = percentage of animals with ulcers

The percentage of ulcer protection will be determined as follows -

\[ \text{% Protective} = \frac{\text{Control mean ulcer index} - \text{Test mean ulcer index}}{\text{Control mean ulcer index}} \times 100 \]

**Determination of free acidity and total acidity**

**Reagents**

- Freshly prepared 0.01N Oxalic acid solution for standardization of sodium hydrosixide
- Freshly prepared 0.01N NaOH Solution
- Toper’s reagents: it is dimethyl amino benzene 0.5% in absolute ethanol
- Freshly prepared 1% phenolphthalein solution.

**Experimental Procedure**

- Gastric juice (1ml) was taken into the 100 ml conical flask, than added 2-3 drops of Tofer’s and titrated with 0.01 N NaOH until all traces of red color disappears and the color of the solution turn yellowish orange.
- The volume of alkali added was noted, this volume corresponds to free acidity.
- Then 2-3 drops of phenolphthalein solution was added and titration was continued until a definite red tinge appears.
- The volume of alkali added was noted which corresponds to total acidity. Acidity was calculated by following formula.

\[ \text{Acidity} = \frac{\text{volume of NaOH} \times \text{Normality of NaOH}}{100} \times 10^2 \]

**Indomethacin Induced Ulcers in Rats**

**Procedure**

Groups of 6 Wistar rats weighing 150–200 g are used. The test drugs are administered orally in 0.1% Tween 80 solution 10 min prior to oral indomethacin in a dose of 20 mg/kg (4 mg/ml dissolved in 0.1% Tween 80 solution). Six hours later, the rats are sacrificed in CO2 anesthesia and their stomachs removed. Formol–saline (2% v/v) is then injected into the totally ligated stomachs for storage overnight. The next day, the stomachs are opened along the greater curvature, then washed in warm water, and examined under a 3- fold magnifier. The lengths of the longest diameters of the lesions are measured and summated to give a total lesion score (in mm) for each animal, the mean count for each group being calculated.

**DATA ANALYSIS**

The results were represented as mean ± SEM of three parallel measurements and statistical significance between treated and control groups were analyzed using one –way analysis of variance (ANOVA) (Graph Pad In Stat 3), analyzed by t test using software sigma* 3.5.

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**Table 2: Animal Protocols For Pylorus Ligation**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Groups</th>
<th>treatment</th>
<th>dose</th>
<th>No. of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1st</td>
<td>Control (2% acacia solution)</td>
<td>1ml/100gm</td>
<td>6</td>
</tr>
<tr>
<td>2.</td>
<td>IIInd</td>
<td>Standard (pantoprazole)</td>
<td>4mg/kg</td>
<td>6</td>
</tr>
<tr>
<td>3.</td>
<td>IIIInd</td>
<td>MEPO</td>
<td>250mg/kg</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>IVth</td>
<td>MEPO</td>
<td>500mg/kg</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 3: Animal Protocols For Indomethein induced ulcers**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Groups</th>
<th>treatment</th>
<th>dose</th>
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<tr>
<td>3.</td>
<td>IIIInd</td>
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</tr>
<tr>
<td>4.</td>
<td>IVth</td>
<td>MEPO</td>
<td>500mg/kg</td>
<td>6</td>
</tr>
</tbody>
</table>

**Antiulcer Activity (Methods For Biochemical Estimations Like Free Acidity, Total Acidity In Gastric Juice) Collection Of Gastric Juice**

Gastric juice was collected from pylorus-ligated rats as mentioned earlier. The gastric juice collected was centrifuged for 1000 rpm for 10 minutes and the volume of gastric juice was measured. This gastric juice was used for biochemical estimations as follows.

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RESULTS

Table 4: Effect of *Plumeria obtusa* stem bark extracts on secretary parameters and ulcer index on pyloric ligated rats.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Treatment (mg/kg)</th>
<th>pH of gastric content</th>
<th>Volume of gastric content (ml/100g)</th>
<th>Free acidity (meq/L/100g)</th>
<th>Total acidity (meq/L/100g)</th>
<th>Ulcer index</th>
<th>% protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle control (1ml/100g)</td>
<td>2.75±0.48</td>
<td>3.5±0.64</td>
<td>19.75±1.2</td>
<td>27.5±1.04</td>
<td>13.5±1.56</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole (4)</td>
<td>6.75±0.48**</td>
<td>1.25±0.25**</td>
<td>7±0.91**</td>
<td>11.25±0.53**</td>
<td>5.25±1.11**</td>
<td>61.11</td>
</tr>
<tr>
<td>3</td>
<td>MEPO (250)</td>
<td>5±0.41*</td>
<td>1.75±0.25*</td>
<td>15±1.58*</td>
<td>22.5±1.44*</td>
<td>8.75±0.85*</td>
<td>35.19</td>
</tr>
<tr>
<td>4</td>
<td>MEPO (500)</td>
<td>6±0.41**</td>
<td>1.5±0.29*</td>
<td>7.5±0.29**</td>
<td>12.5±0.64**</td>
<td>6±0.41**</td>
<td>55.56</td>
</tr>
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</table>

All values are mean ± SEM, n=6, each group compared by control group. p < 0.01**, p < 0.05* Data is analyzed by ANOVA (Dunnett t test).

Graph 1: Percentage Protection In Pyloric Ligation Induced Ulcer Model

All values are mean ± SEM, n=6 in each group, p < 0.01**, p <0.05**, F (3,12) = 12.275, Data is analyzed by ANOVA (Dunnett t test).

Table 5: Effect of *Plumeria obtusa* stem bark extracts on Ulcer index and % protection on Indomethcin induced ulcer in rats

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Groups</th>
<th>Treatment</th>
<th>dose</th>
<th>Ulcer index</th>
<th>% protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ist</td>
<td>Control (2% acacia solution)</td>
<td>1ml/100gm</td>
<td>13.25±1.11</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>IInd</td>
<td>Standard (pantoprazole)</td>
<td>4mg/kg</td>
<td>5±0.91**</td>
<td>62.26</td>
</tr>
<tr>
<td>3.</td>
<td>IIIrd</td>
<td>MEPO</td>
<td>250mg/kg</td>
<td>8.75±0.85*</td>
<td>33.96</td>
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<tr>
<td>4.</td>
<td>IVth</td>
<td>MEPO</td>
<td>500mg/kg</td>
<td>6±1.08**</td>
<td>54.72</td>
</tr>
</tbody>
</table>

All values are mean ± SEM, n=6, each group compared by control group, p < 0.01**, p <0.05**, F (3, 12) = 13.768, Data is analyzed ANOVA
**Graph 2**: Percentage Protection In Indomethacin Induced Ulcer Models

All values are mean ± SEM, n=6 in each group, p < 0.01**, p < 0.05*, F (3, 12) = 13.768, Data is analyzed by ANOVA (Dunnett t test).

**Fig: 1**: Healing of Pylorus Ligated Induced Gastric Ulcer
DISCUSSION
The etiology of the peptic ulcer unknown in most of the cases, yet it is generally accepted that it results from imbalance between aggressive factors and the maintenance of mucosal integrity through the endogenous defense mechanism. Therapeutic agents are used to inhibit the gastric acid secretion or to boost the mucosal defense mechanisms by increasing mucosal production, stabilizing the surface epithelial cells or interfering with the prostaglandin synthesis. The causes of gastric ulcer pyloric ligation are believed to be due to stress induced increased in gastric hydrochloric acid secretion and/or stasis of acid of and the volume of secretion is also an important factor in the formation of ulcer due to exposure of the unprotected lumen of the stomach to the accumulating acid (Dhuley,1999). Pylorus ligation induced ulcer was used to study the effect of fruit extract on gastric acid secretion and mucus secretion. The ligation of the pyloric end of the stomach causes accumulation of gastric acid in the stomach. This increase in the gastric acid secretion causes ulcer in the stomach. The original shay rat model involves fasting of rat for overnight followed by ligation of pyloric end of the stomach. The ulcer index is determined 19hrs after pylorus ligation. The lesions produced by this method are located in the lumen region of the stomach.

In this study methanolic extracts of Plumeria obtusa stem bark and pantoprazole showed a significant reduction in ulcer index and percent protection when compared to control (p<0.01, p<0.01, p<0.05); this suggested that it is having an antisecretory effect. The results showed in the table. Anti-inflammatory drug like Indomethacin administered in toxic dose (20mg/kg), produce visible gastric ulcers in animals. Indomethacin is an potent inhibitor of prostaglandin biosynthesis. Prostaglandins are known to play an important role in maintaining mucosal integrity. An increase in certain endogenous prostaglandins can enhance gastric mucosal resistance to ulcerogenic agents. The mechanism in prostaglandin action are multiple, including stimulation of mucus and bicarbonate output.

Gastric mucosal blood flow decreasing gastric motility, increasing the release of endogenous mediators of gastric injury vasoactive amines and leukotrienes and stimulation of cellular growth and repair. In the present study, the effect of the extract on prostaglandin biosynthesis was not evaluated; but an increase in resistance to the necrotizing effect of Indomethacin was noted.

In this methanolic extracts of Plumeria obtusa stem bark and pantoprazole showed a significant reduction ulcer index and percent protection when compared to control (p<0.01, p<0.05); the results showed in the table. The animals become very weak after 7 hours of administered of Indomethacin (20mg/kg) and they showed symptoms of severe diarrhea and their stools were black in color.

In this study methanolic extracts of Plumeria obtusa stem bark and pantoprazole showed a significant reduction in Ulcer index, and percent protection when compared to control (p<0.05, p<0.01); this suggested that this antiulcer effect of methanolic extracts of Plumeria obtusa stem bark extract due to reductions in gastric acid and gastric cytoprotection.
The percentage of ulcer inhibition was observed in standard, MEPO 250mg/kg & MEPO 500mg/kg is 61.11 %, 35.19% and 55.56% respectively. Similar results were observed in the indomethacin induced ulcer protocol displayed in the table. The plant extracts heal indomethacin induced stomach ulceration by their triterpenoids action & inhibition was observed 62.26%,33.96% and 54.72% in the animal treated with MEPO 250mg/kg, MEPO500mg/kg & standard drug respectively. Plumeria obtusa stem bark extracts and standard drug respectively. No sign of toxicity & side effects was observed after the administration of test and standard drugs.

CONCLUSION
The results of whole study has been concluded that the Plumeria obtusa stem bark have Various phytoconstituents like triterpenoids, flavonoids, carbohydrate, essentialoil, glycosides & alkaloids. The observation emanated in the present study indicated that the extracts of Plumeria obtusa stem bark are effective against ulcers. The methanolic extracts of Plumeria obtusa stem bark were effective in increasing the healing of gastric ulcers induced by pylorus ligation, indomethacin. The results indicate antiulcer effects extracts of Plumeria obtusa stem bark are due to reduction in gastric acid secretion & gastric cytoprotection and proton pump inhibition mechanism. Ulcer caused by Pylorus ligation are due to increased accumulation of gastric acid and pepsin leading auto digestion of gastric mucosa so the effects of phenolic acids on gastric lesions induced by pylorus ligation are displayed in table 1 pre-treatment with Plumeria obtusa stem bark extracts in dose of MEPO 250mg/kg & 500 mg/kg significantly diminished the ulcer index, total ulcer area and the % protection of ulcer compared with control group (p<0.05, p<0.001).

To evaluate the mechanism by which Plumeria obtusa stem bark extract increased the healing of gastric ulcers further studies on their effect on gastric secretion & gastric cytoprotection was evaluated using different gastric and duodenal models.

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