EVALUATION OF ANTIULCEROGENIC PROPERTY OF QUERCETIN IN ALBINO RATS
Ramesh H, Dattatri A. N, Patil R. S.

1. Associate Professor, Department of Pharmacology, Karnataka Institute of Medical Sciences (KIMS), Hubli.
2. Professor, Department of Pharmacology, Karnataka Institute of Medical Sciences (KIMS), Hubli.
3. Tutor, Department of Pharmacology, Karnataka Institute of Medical Sciences (KIMS), Hubli.

CORRESPONDING AUTHOR
Dattatri A. N,
Professor of Pharmacology,
KIMS, Hubli,
E-mail: an_dattatri@yahoo.com
Ph: 0091 9902354622.

ABSTRACT: OBJECTIVES: To study the possible antiulcerogenic property of quercetin, and to compare it with standard drug ranitidine. METHODS: The study was carried out in two ulcer models i.e alcohol model and indomethacin model. Both the models consist of 3 groups (control, standard control, test compound groups) of 6 rats each. The control group received only ulcerogen whereas the standard control group and test compound group were pretreated with ranitidine and quercetin respectively for 5 days before exposure to ulcerogen. On 5th day the rats were sacrificed, stomach dissected out and opened. Ulcer grading was done and ulcer index was calculated. Statistical analysis was done by using Student’s t test. p value of < 0.05 was considered for statistical significance. RESULTS: In Alcohol model, the rats pretreated with quercetin showed highly significant protection (p < 0.001) when compared to control group and significant protection when compared to ranitidine pretreated group (p < 0.05). In indomethacin model, both quercetin and ranitidine pretreated groups showed significant protection when compared to control group (p < 0.01). CONCLUSION: Present study indicates that quercetin is highly effective in preventing ethanol-induced gastric mucosal damage (better than ranitidine) and equally effective as ranitidine in preventing indomethacin-induced gastric mucosal damage.

KEY WORDS: Quercetin, Ranitidine, Gastric ulcer, Ethanol, Indomethacin.

INTRODUCTION: Peptic ulcer is very common disease. It kills few but troubles many. Peptic ulcer results probably due to an imbalance between aggressive factors (acid, pepsin, H. pylori) and defensive factors (gastric mucus, prostaglandins and bicarbonate secretion). Whatever may be the cause of peptic ulcer, it is the gastric acid that prevents ulcer healing and maintain the ulcer. Therefore most of the drugs available for treatment of peptic ulcer either neutralize the secreted acid or decrease the acid secretion.

There is growing body of experimental data that suggests the generation of oxygen derived free radicals and lipid peroxidation as one of the mechanisms in pathogenesis of peptic ulcer. Hence there is a need to develop drugs that are directed towards scavenging of these free radicals and produce antulcerogenic effect.

Quercetin is a bioflavonoid found in many plants. It is widely distributed in edible fruits and vegetables. It is weakly toxic drug and has been used in the treatment of allergy, bee sting and ulcer with no serious side effects in adults. It is a very strong antioxidant, prevents oxidant injury and cell death by several mechanisms such as scavenging oxygen free radicals.
antioxidant potential is four times that of vitamin E. It is potent inhibitor of lipid peroxidation. It is also a proton pump inhibitor. Because of these properties of quercetin this scientific study is undertaken to evaluate its antiulcerogenic property in albino rats.

MATERIALS AND METHODS: Animals: 36 albino rats of Wistar strain of either sex weighing 150 - 200 g were selected from central animal house of Karnataka Institute of Medical sciences, Hubli. The animals were kept on standard diet and allowed food and water ad libitum. The experimental protocol was approved by the institutional animal ethical committee.

MATERIALS:
Drugs:
• Ethanol (99.9%) – As ulcerogenic agent.
• Indomethacin (Microlabs Ltd) – As ulcerogenic agent.
• Ranitidine (JB Chemicals & Pharmaceuticals Ltd) – As standard control.
• Quercetin (Sisco Research Laboratories) – As test compound.

Dose and duration and administration of drugs
• Ethanol (99.9%) – A dose of 1 ml.
• Indomethacin – 20 mg/kg, 2 doses at an interval of 15 hrs.
• Ranitidine – 25 mg/kg, once daily for 5 days.
• Quercetin – 50 mg/kg, once daily for 5 days.
(Quercetin powder freshly dissolved in distilled water during treatment)
All drugs are administered intragastrically through infant feeding tube.

METHODS:
1) Ethanol induced gastric ulcers
In this method, 18 albino rats were divided into 3 groups with 6 rats in each group.
Group I A (Control) : Received ulcerogen only.
Group I B (Standard control): Received ranitidine once daily for 4 days and 30 minutes prior to ulcerogen on 5th day
Group I C (Test compound) : Received quercetin once daily for 4 days and 30 minutes prior to ulcerogen on 5th day

The animals in all the groups were fasted for 24 hrs prior to the administration of ulcerogen with water ad libitum.
Animals were sacrificed 4 hrs after the administration of ethanol by dislocating cervico-atlanto joint. The anterior abdominal wall was opened and the stomach was dissected out.

2) Indomethacin induced gastric ulcers
In this method 18 albino rats were divided into 3 groups of 6 rats each.
Group II A (Control) : Received ulcerogen only.
Group II B (Standard control): Received Ranitidine once daily for 3 days and 30 minutes prior to ulcerogen on 4th & 5th day
Group II C (Test compound) : Received quercetin once daily for 3 days and 30 minutes prior to ulcerogen on 4th & 5th day.
The animals in all the groups were fasted for 24 hrs prior to the administration of ulcerogen with water ad libitum. Two doses of indomethacin were administered at an interval of 15 hrs.

Animals were sacrificed 6 hrs after the second dose of indomethacin by dislocating cervico-atlanto joint. The anterior abdominal wall was opened and the stomach was dissected out.

In both the methods, the dissected stomachs were opened along the greater curvature, the number of ulcers was noted and grading of ulcers was done according to the method described by Laurence and Bacharach:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of gastric mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Scattered hemorrhage spots</td>
</tr>
<tr>
<td>2</td>
<td>Hemorrhagic spots + ulcer</td>
</tr>
<tr>
<td>3</td>
<td>Deep hemorrhagic spots + ulcer</td>
</tr>
<tr>
<td>4</td>
<td>Perforation</td>
</tr>
</tbody>
</table>

The ulcer index was calculated for each group by the method of Sunita and Devdas:

\[
\text{Ulcer index} = \text{Arithmetic mean of the intensity in a group} + \left( \frac{\text{Ulcer positive No.} \times 2}{\text{Total No. of rats}} \right)
\]

Statistical analysis: The results were interpreted by paired Student’s t test. A p value of < 0.05 was considered as statistically significant.

RESULTS: Group I A: In this group, the total score, mean score, ulcer incidence and ulcer index were 16, 2.67, 100% and 4.6 respectively. (Table 1)

Group I B: In this group there was reduction in total score, mean score, ulcer incidence and ulcer index as compared to control group. The p value was significant (p < 0.05) (Table 1)

Group I C: In this group there was reduction in total score, mean score, ulcer incidence and ulcer index. The p value was highly significant compared to control group (p < 0.001) and significant as compared to standard control group (p < 0.05). (Table 1)

Group II A: In this group, the total score, mean score, ulcer incidence and ulcer index were 15, 2.5, 100% and 4.5 respectively. (Table 2)

Group II B: In this group there was reduction in total score, mean score, ulcer incidence and ulcer index as compared to control group. The p value was significant (p < 0.01) (Table 2)

Group II C: In this group there was reduction in total score, mean score, ulcer incidence and ulcer index as compared to control group. The p value was significant (p < 0.01). But the total score and ulcer index were slightly higher as compared to standard control group, and it was not statistically significant (p > 0.05). (Table 2)

DISCUSSION: Present study was undertaken to evaluate the protective effect of quercetin against ethanol and indomethacin-induced gastric mucosal damage.
Ethanol-induced gastric mucosal damage was seen in the glandular portion of stomach as elongated red streak. The fore-stomach or rumen (non-glandular portion) was spared. This may be due to squamous epithelium that covers its surface\textsuperscript{15}. The ulcer lesions were confined to the mucosal crests, and this may be due to the presence of these folds at the time of exposure to ethanol\textsuperscript{16}. Ethanol-induced damage to gastric mucosa is associated with a significant production of free radicals\textsuperscript{17}, leading to increased lipid peroxidation. This causes damage to cell membranes.

In our study, pretreatment with quercetin in the dose of 50 mg/kg reduced total score, ulcer incidence and ulcer index as compared to control group (I A). The p value was < 0.001 (highly significant).

Quercetin is a flavonoid and has potent lipid peroxidation inhibiting property\textsuperscript{10,11}. As lipid peroxidation is suggested to be one of the important mechanisms of Ethanol induced gastric ulcer, quercetin probably acts by inhibiting the lipid peroxidation.

Even though ranitidine pretreated animals (I B) showed significant reduction in total score, ulcer incidence and ulcer index as compared to control group (I A) (p < 0.05), it was inferior when compared to quercetin pretreated group (p < 0.05). This indicates the superiority of quercetin over ranitidine in preventing ethanol-induced gastric mucosal damage.

Ranitidine acts by blocking H\textsubscript{2} receptors and thus inhibits gastric acid secretion. Ethanol-induced ulcers occur instantaneously irrespective of the acid content in the stomach. As the mechanism of gastric mucosal damage by ethanol is different, H\textsubscript{2} blockers are only partially effective in inhibiting ethanol-induced gastric mucosal damage. This finding correlates with the study conducted by Robert et al\textsuperscript{15}.

Normal amount of gastric acid is also necessary for the development of gastric ulcers produced by NSAIDs\textsuperscript{15}. In the present study, in indomethacin-induced gastric ulcer model, the total score, ulcer incidence and ulcer index in ranitidine pretreated animals (II B) were significantly reduced as compared to control group (II A) (p < 0.01). As the H\textsubscript{2} blockers reduce the gastric acid secretion, they are effective in preventing the gastric mucosal damage produced by NSAIDs. In quercetin pretreated animals (II C) even though the total score, ulcer incidence and ulcer index were significantly reduced when compared to control group (p < 0.01), the total score and ulcer index were only slightly higher as compared to ranitidine pretreated group (statistically not significant; p > 0.05). So the protection given by quercetin against indomethacin-induced gastric mucosal damage is nearly comparable to that by ranitidine.

In a study conducted by Rao CV et al, quercetin significantly decreased the acid and pepsin output of gastric contents\textsuperscript{11}. In another study conducted by Elango V et al, quercetin was shown to inhibit the proton pump and increase the synthesis of local prostaglandins\textsuperscript{10}. Thus it appears that quercetin exert its gastric mucosal protection against indomethacin-induced lesions by decreasing acid and pepsin content of the stomach and by increasing local prostaglandin synthesis. In another study, Yoshikawa et al reported the role of active oxygen species and lipid peroxidation in the pathogenesis of gastric mucosal injury induced by indomethacin\textsuperscript{18}. As quercetin is a potent inhibitor of lipid peroxidation, it prevents indomethacin-induced gastric mucosal damage.

In our study quercetin has been found to be better than ranitidine in preventing ethanol-induced gastric mucosal damage and nearly equally effective as ranitidine in preventing indomethacin-induced gastric mucosal damage.
ACKNOWLEDGEMENT: The authors wish to thank Mrs. S. R. Itagimath for statistical help.

REFERENCES:

Table 1 Ethanol-induced gastric ulcers

<table>
<thead>
<tr>
<th></th>
<th>Group I A (Control group)</th>
<th>Group I B (Standard control group)</th>
<th>Group I C (Test compound group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>16</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Mean score</td>
<td>2.67</td>
<td>2.0</td>
<td>0.67</td>
</tr>
<tr>
<td>Total No. of rats with ulcer</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer incidence</td>
<td>100%</td>
<td>66.66%</td>
<td>16.66%</td>
</tr>
<tr>
<td>Ulcer index</td>
<td>4.6</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.516</td>
<td>0.894</td>
<td>0.816</td>
</tr>
</tbody>
</table>

*\( p < 0.001 \) when I C is compared to I A

**\( p < 0.05 \) when I B is compared to I A & I C is compared to I B

Table 2 Indomethacin-induced gastric ulcers

<table>
<thead>
<tr>
<th></th>
<th>Group II A (Control group)</th>
<th>Group II B (Standard control group)</th>
<th>Group II C (Test compound group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>15</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Mean score</td>
<td>2.5</td>
<td>01</td>
<td>1.33</td>
</tr>
<tr>
<td>Total no of rats with ulcer</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ulcer incidence</td>
<td>100%</td>
<td>33.33%</td>
<td>33.33%</td>
</tr>
<tr>
<td>Ulcer index</td>
<td>4.5</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.548</td>
<td>0.814</td>
<td>0.516</td>
</tr>
</tbody>
</table>

*\( p < 0.01 \) when II B is compared to II A & II C is compared to II A