Antiulcerogenic activity of *Satavari mandur*—An Ayurvedic herbo-mineral preparation

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*Satavari mandur* (SM) is a herbo-mineral preparation containing *Asparagus racemosus*, which finds mention in ancient Indian texts for treatment of gastric ulcers. The ulcer protective effect of SM, 125-500 mg/kg given orally, twice daily for three, five and seven days, was studied on cold restraint stress-induced gastric ulcer in rats. The effective regimen was found to be 250 mg/kg given for five days and hence was used for further experiments. SM showed significant protection against acute gastric ulcers induced by pyloric ligation but was ineffective against aspirin- and ethanol-induced ulcers. Further, gastric juice studies showed that, SM significantly increased the mucosal defensive factors like mucus secretion, but had little or no effect on offensive factors like acid and pepsin secretion.

*Satavari Mandur* (SM) is an Ayurvedic herbo-mineral formulation used since 19th century A.D. for treatment of peptic ulcer. In the medieval period herbo-mineral preparations were introduced in the management of different diseases to increase the stability of the herbal formulations and to reduce the doses. In *Cakradatta*, an Ayurvedic text, SM has been reported to be used in parinamasula, which may be correlated with gastric or duodenal ulcers. The main ingredient of the formulation is juice of satavari (*Asparagus racemosus*. F. Liliaceae) which has been reported to possess several pharmacological activities. Satavari has also been reported to be useful in gastric and duodenal ulcers by other Ayurvedic texts like *Susruta samhita*. We had earlier reported the antiulcerogenic activity of juice of roots of Satavari. Further, as SM is widely used in Ayurvedic practice, we thought that it would be worthwhile to evaluate the antiulcerogenic activity of SM.

Factors related to ulcerogenesis, results in imbalance between offensive and defensive mucosal factors. Several drugs used in the treatment of ulcers reduce or neutralize the offensive acid secretions. Other drugs like carbenoxolone, sucralfate and prostaglandin analogs increase the defensive factors without affecting the offensive acid secretion; these are termed as cytoprotective drugs. However, these have not been widely used in therapy. Several natural drugs have been reported to poses anti-ulcerogenic activity by virtue of their predominant effect on mucosal defensive factors.

In view of these facts, the present study also incorporates the effect of SM on various offensive factors like acid-pepsin secretion and the important defensive factor like mucin secretion apart from the study of its antiulcerogenic activity.

**Materials and Methods**

**Animals**—Albino rats (C-F strain) of either sex weighing between 150 and 180 g were procured from the central animal house of the Institute and housed in well ventilated colony cages in the departmental animal house at 25°C ± 2°C and 45-56% RH, 10:14 hr L:D cycles for one week for acclimatization. The animals were fed with standard rodent pellet diet (Hind Lever) and water ad libitum.

**Collection of plant**—*Asparagus racemosus* of cultivated variety was obtained during the month of December from the Ayurvedic gardens of the Institute and was identified with the reference herbarium maintained in the Department of Dravyaguna. Roots (1 kg) were reduced in size; crushed and 650 ml of juice thus obtained was filtered. The fresh juice was used for the preparation of SM.

**Preparation of satavari mandur**—The ingredients of SM are 1. Satavari juice (500 ml), 2. Mandur bhasma (500 g), 3. Cow’s milk (500 ml), 4. Curd prepared from 500 g and 5. cow’s ghrita (ghee) 250 g.
SM was prepared as recommended in the Ayurvedic literature. Milk (500 ml) was boiled in a stainless steel container until it became semisolid with 1/3 reduction in the volume. Curd was added to it, stirred followed by addition of juice of satavari. After the watery portion evaporated out on boiling, mandur bhasma was added till the preparation turned into a paste. Mandur bhasma was prepared as reported earlier for Louha bhasma. Briefly, Mandur bhasma is heated iron sludge used after purification. These sludges when kept in contact with soil for sometime becomes brittle and rusty and are similar to Ferri peroxidum and Ferrioxidum precipitatum Fascum, mentioned in the Indian and British Pharmacopoeias. These were then purified by heating in charcoal wood and immersing in cow’s urine. This procedure was repeated seven times. The sodhana (purified iron) thus obtained was made into a paste with cow’s urine and was used as mandur in the preparation. The amount of satavari mandur obtained was 900 g and the preparation was used within 7 days.

**Experimental study**

Initially to find out the optimal dose and duration of treatment, SM in doses of 125, 250 and 500 mg/kg and ranitidine (RTD), the reference drug in the dose of 2.5 mg/kg were administered, orally, twice daily at 1000 and 1600 hrs for three, five or seven days.

a) Cold-restraint stress (CRS) induced ulcers: On 6th day of experiment in 18 hr fasted rats, CRS was given by strapping the rats on a wooden plank and keeping them at 4°-6°C for 2 hr. The animals were then sacrificed by cervical dislocation on the day of the experiment. The stomach was taken out and cut open along the greater curvature and ulcers were scored by a person unaware of the experimental protocol as described earlier. Statistical analysis was done using Wilcoxon Rank Sum test.

The optimal dose of 250 mg/kg of SM, given twice for five days, was used for further anti-ulcer and gastric secretion studies.

b) Ethanol (EtOH)-induced ulcers: The gastric ulcers were induced in rats by administering absolute EtOH (99.8%, 1 ml/200 g, 1 hr). The animals were sacrificed by cervical dislocation, stomach was incised along the greater curvature and was examined for ulcers. The ulcer index was scored, based upon the product of length and width of the ulcers present in the glandular portion of the stomach (mm²/rat). Statistical analysis of data was done by using unpaired Student’s t test.

c) Aspirin (ASP)-induced ulcers: ASP in dose of 200 mg/kg (20 mg/ml) was administered to the animals and ulcers were scored after 4 hr as described for CRS-induced ulcers.

d) Pylorus-ligated (PL)-induced ulcers: Drugs were administered for 5 days as described above. After the last dose on day 5, the rats were kept for 18 hr fasting and care was taken to avoid coprophagy. On 6th day of experiment, animals were anaesthetized using pentobarbitone (35 mg/kg, IP), the abdomen was opened and pylorus ligation was done without causing any damage to its blood supply. The stomach was replaced carefully and the abdominal wall was then closed in two layers with interrupted sutures. The animals were deprived of water during the post-operative period. After 4 hr, stomachs were dissected out and contents were collected into tubes for estimation of biochemical parameters. The ulcers were scored as described under CRS-induced ulcers.

**Gastric secretion study**

Studies on offensive factors such as acid and pepsin, defensive factors such as mucin secretion and cell shedding were carried out in gastric secretion. The gastric juice was collected 4 hr after PL and centrifuged for 5 min at 2000 rpm. The supernatant was collected and the volume of gastric juice was expressed as ml/100 g body weight. Acid concentration and output were determined by titrating with 0.01 N NaOH, using phenolphthalein as indicator and is expressed as μEq/ml and μEq/4 hr respectively. Peptic activity was determined using hemoglobin as substrate and was expressed as μmol/ml and μmol/4 hr for concentration and output respectively. Dissolved mucosubstances were estimated in 90% alcoholic precipitate of the gastric juice. The precipitate, thus obtained was either dissolved in 1 ml of 0.1 N NaOH or 1 ml of 0.1 N H₂SO₄. The former was used for the estimation of protein¹⁸, total hexoses, hexosamine and fucose, while the latter was used for the estimation of sialic acid as described earlier¹⁹. The results were expressed in μg/ml of gastric juice. The ratio of total carbohydrate (TC) (sum of total hexoses, hexosamine, fucose and sialic acid) to protein (P) was taken as the index of mucin activity¹⁹.

**Results**

Satavari mandur (SM) 125-500 mg/kg, given orally, twice daily for 3.5 or 7 days showed dose-dependent protective effect against gastric ulcers induced by cold restraint stress (CRS). SM showed sig-
significant antiulcer effect in the dose of 250 and 500 mg/kg after 3 and 5 days treatment and in all doses after 7 days treatment (Table 1). There afterwards the effective dose of 250 mg/kg when given for 5 days showed significant antiulcer activity against pyloric ligation-induced gastric ulcers but was however, ineffective against aspirin and ethanol induced gastric ulcers (Table 2). The reference ranitidine was effective against all the above ulcer models except ethanol-induced ulcers.

On gastric secretion, SM did not show any effect on offensive acid-pepsin secretion (Table 3). Ranitidine decreased the volume, acid and pepsin output. SM significantly increased the defensive mucin secretion in terms of TC:P ratio of the gastric juice. This was mostly due to increases in individual carbohydrates although insignificant and decreases in protein content of the gastric juice (Table 4). However, ranitidine only showed a tendency to increase in mucin secretion.

**Discussion**

SM in the doses of 125, 250 and 500 mg/kg given twice daily for 3, 5 and 7 days, showed significant dose-dependent ulcer protective effect against cold restraint stress. Moreover, CRS model was chosen for the initial study to ascertain the dose and duration of treatment because satavari, the main ingredient of SM has been reported to have adaptogenic properties. In accordance SM was found to be effective in stress-induced ulcers. Stress plays an important role in aetiology of gastric ulceration. Apart from psychological factors, stress-induced ulcers are also caused by number of other physiological factors. It is then imperative that SM might also act on other factors apart from its anti-stress effects.

SM was also effective against PL-induced gastric ulcers. PL-induced ulcers are thought to be due to increase in acid-pepsin accumulation due to pyloric obstruction and subsequent mucosal digestion. Hence as SM did not show any effect on acid-pepsin secretion, its anti-ulcer effect could involve predominantly mucosal defensive factors. SM showed tendency to increase in defensive mucin secretion quantified in terms of TC:P ratio of the gastric juice. TC:P ratio is taken as a reliable marker for mucin secretion. Mucin is viscous glycoprotein constituting of major part of mucus, an important pre-epithelial factor. This also acts as a first line of defense against ulcerogenesis. Decrease in protein content also signifies decrease in leakage from the mucosal cells indicating increased mucosal resistance. In contrast, ranitidine significantly decreased the acid-pepsin secretion and had minimal effects on mucin secretion. Being an H2

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### Table 1 — Effect of satavari mandur (SM) and ranitidine (RTD) on 2 hr cold restraint stress-induced gastric ulcers in rats

[Values are mean ± SE of 6 animals in each group]

<table>
<thead>
<tr>
<th>Treatment (mg/kg, po, bd ×5 days)</th>
<th>3 days</th>
<th>5 days</th>
<th>7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>32.8 ± 5.4</td>
<td>28.8 ± 4.7</td>
<td>31.8 ± 5.1</td>
</tr>
<tr>
<td>SM 125</td>
<td>19.5 ± 6.3</td>
<td>16.8 ± 3.7</td>
<td>17.5 ± 3.9a</td>
</tr>
<tr>
<td>250</td>
<td>15.8 ± 4.3a</td>
<td>15.5 ± 2.9a</td>
<td>16.8 ± 3.1a</td>
</tr>
<tr>
<td>500</td>
<td>9.0 ± 2.3a</td>
<td>13.8 ± 2.3a</td>
<td>8.7 ± 4.9b</td>
</tr>
<tr>
<td>RTD 2.5</td>
<td>14.2 ± 3.3a</td>
<td>10.7 ± 4.7a</td>
<td>9.2 ± 3.7b</td>
</tr>
</tbody>
</table>

P values: *<0.05, b<0.01

### Table 2 — Effect of SM and RTD on 4 hr pylorus ligation (PL), ethanol (EtOH, 100%, 1 ml/200 g, po, 1 hr)- and aspirin (ASP, 200 mg/kg, po, 4 hr)-induced gastric ulcers in rats

[Values are mean ± SE of 6 animals in each group]

<table>
<thead>
<tr>
<th>Treatment (mg/kg, po, bd ×5 days)</th>
<th>ASP</th>
<th>EtOH</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17.5 ± 3.2</td>
<td>28.7 ± 3.1</td>
<td>16.0 ± 3.1</td>
</tr>
<tr>
<td>SM 250</td>
<td>13.6 ± 4.1</td>
<td>23.2 ± 3.7</td>
<td>6.3 ± 2.9a</td>
</tr>
<tr>
<td>RTD 2.5</td>
<td>4.7 ± 1.7b</td>
<td>22.3 ± 3.7</td>
<td>4.2 ± 2.1a</td>
</tr>
</tbody>
</table>

P values: *<0.05, b<0.01

### Table 3 — Effect of SM and RTD on gastric juice volume, acid and pepsin secretion in 4 hr PL rats

[Values are mean ± SE of 6 animals in each group]

<table>
<thead>
<tr>
<th>Treatment (mg/kg, po, bd ×5 days)</th>
<th>Volume (ml/100 g)</th>
<th>Concentration (µEq/ml)</th>
<th>Acid Output (µEq/4h)</th>
<th>Concentration (µmol/ml)</th>
<th>Pepsin Output (µmol/14h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.83 ± 0.06</td>
<td>140.0 ± 7.3</td>
<td>126.3 ± 19.8</td>
<td>659.0 ± 78.0</td>
<td>563.0 ± 86.0</td>
</tr>
<tr>
<td>SM 250</td>
<td>1.25 ± 0.19</td>
<td>145.0 ± 16.6</td>
<td>189.9 ± 24.2</td>
<td>610.0 ± 55.0</td>
<td>759.0 ± 115.0</td>
</tr>
<tr>
<td>RDT 2.5</td>
<td>0.40 ± 0.07b</td>
<td>120.0 ± 9.7</td>
<td>48.1 ± 14.6b</td>
<td>559.0 ± 70.0b</td>
<td>223.0 ± 70.0b</td>
</tr>
</tbody>
</table>

P values: *<0.05, b<0.01
receptor antagonist, the activity of ranitidine can be ascribed to its effects on offensive factors rather than on the defensive factors.

However, SM was ineffective against aspirin and ethanol-induced gastric ulcers. Aspirin has direct irritant effect and thereby increases the H⁺ ion transport. The mucosal epithelial factors like mucin, surface-active phospholipids, bicarbonate secretion, mucosal proliferation are decreased. It also produces microvascular damage by formation of free radicals. It may be possible that SM was not able to overcome all these factors particularly prostaglandins, even though it has significantly increased mucin secretion. Ulcerations by ethanol are caused due to perturbations of superficial mucosal cells, notably the mucosal mast cell leading to release of vasoactive mediators including histamine, thus causing damage to gastric mucosa. Mucosal blood flow has been attributed to be an important factor in the damage caused by alcohol and is modulated by prostaglandins. The ineffectiveness of SM, to protect against mucosal damage caused by ethanol might be due to its minimal effect on prostaglandins apart from other factors. Ranitidine was also ineffective against ethanol-induced ulcers. This might be due to the fact that ethanol-induced ulcers are independent of luminal acid and as the anti-ulcer activity of ranitidine is basically based on its ability to block acid secretion it proved to be ineffective.

Hence, the anti-ulcer effect of SM might be due its predominant effect on the mucosal defensive factors rather than offensive factors. Further studies on the mucosal defensive factors like nitric oxide and cAMP etc., could provide more details on the activity of SM.

Acknowledgement

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Table 4 — Effect of SM and RTD on gastric juice mucin secretion (µg/ml) in 4 hr PL rats

<table>
<thead>
<tr>
<th>Treatment (mg/kg, po, bd×5 days)</th>
<th>Protein (P)</th>
<th>Total hexoses (a)</th>
<th>Hexose amino (b)</th>
<th>Fucose (c)</th>
<th>Sialic acid (d)</th>
<th>TC (a+b+c+d)</th>
<th>TC:P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>446 ± 43</td>
<td>248 ± 39</td>
<td>143 ± 14</td>
<td>91 ± 13</td>
<td>36 ± 3</td>
<td>519 ± 53</td>
<td>1.11 ± 0.09</td>
</tr>
<tr>
<td>SM 250</td>
<td>346 ± 33</td>
<td>289 ± 43</td>
<td>120 ± 19</td>
<td>101 ± 10</td>
<td>47 ± 8</td>
<td>558 ± 60</td>
<td>1.61 ± 0.18³</td>
</tr>
<tr>
<td>RTD 2.5</td>
<td>431 ± 24</td>
<td>262 ± 30</td>
<td>126 ± 18</td>
<td>79±8</td>
<td>36 ± 5</td>
<td>503 ± 47</td>
<td>1.18 ± 0.07</td>
</tr>
</tbody>
</table>

P value: <0.05

References


23 Hase T, Moss B J, Microvascular changes of gastric mucosa in the development of stress ulcer in rats, Gastroenterology, 65 (1973) 224.


