Effect of *Ruta graveolens* L. and *Euphorbia peplus* L. anti-inflammatory extracts on nutritional status of rats and the safety of their use

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Received 26 September 2000; revised 23 August 2001

A significant increase in body weight with remarkable increase in total food intake and significant increase in protein efficiency ratio were observed following oral administration of *R. graveolens* ether extract (500 mg/kg body wt) to growing rats for 3 weeks. Serum albumin was significantly decreased after administration of declofenac (15 mg/kg body wt). Albumin/globulin ratio decreased significantly on administration of *E. peplus* ether extract (500 mg/kg body wt). No significant changes were observed in other biochemical and nutritional parameters on administration of either of the extracts or declofenac. However, only a significant elevation of alkaline phosphatase was noticed during treatment with *R. graveolens*. The results suggest that both plant extracts have no harmful effect on nutritional status and are safe towards kidney functions, while *Euphorbia* is more safe than *Ruta* in relation to liver functions.

*Euphorbia peplus* L. (Euphorbiaceae) the most common Euphorbia in Egypt was used long ago for the treatment of asthma and catarrh. *Ruta graveolens*, L (Rutaceae) has been reported to possess, cytotoxic and hypotensive effects.

Ether extracts of both *R. graveolens* and *E. peplus* have recently been reported to have anti-inflammatory activity. Non polar extract of *E. peplus* contains pentacyclic triterpenoids, triterpenols and fatty acid esters while that of *R. graveolens* is rich in coumarins compounds mainly bergapten, xanthotoxin and umbelliferone.

Low serum iron, low haemoglobin concentration, reduced serum albumin level, elevation of alpha and gamma globulin with increased level of serum alkaline phosphatase and serum creatinine are some of the biochemical parameters that are affected in chronic inflammatory diseases specially rheumatoid arthritis, which is usually associated with anorexia and weight loss.

The aim of the present research is to study the effect of newly identified anti-inflammatory agents (ether extracts of *E. peplus* and *R. graveolens*) on the above parameters to determine the safety of their use and at the same time to assess the nutritional status during treatment with such agents in comparison to synthetic anti-inflammatory drug, declofenac.

Materials and Methods

Rats—White albino rats of either sex, weighing 40-60g body weight were used. The animals were kept individually in wire bottomed cages at room temperature (25° ± 2°C).

Diet—Balanced diet consisting of 10.3% casein (10% protein), 15% corn oil, 23.5% sucrose, 46.7% starch, 3.5% salt mixture and 1% vitamin mixture was fed to rats.

Plants—Aerial parts of *Ruta graveolens*, and the herb of *Euphorbia peplus*, were collected from the Orman Garden, Giza, Egypt and authenticated by Miss Badia Diwan, Agriculture Engineer, Ministry of Agriculture, Cairo, Egypt. A voucher specimen has been deposited in the NRC Herbarium.

Drug—Declofenac was used as reference, non steroidal anti-inflammatory drug.

Preparation of plants’ extracts—The air-dried powders of *R. graveolens* and *E. peplus* were separately extracted with petroleum ether (40°-60°C) followed by ether in a continuous extraction apparatus until exhaustion. The solvent was stripped off by distillation under reduced pressure at a temperature below 40°C and dried to constant weight in a vacuum desiccator over anhydrous calcium chloride. Each experiment was repeated thrice. The mean percentage yields of the ether extracts were -1.7 and 0.9 for *Ruta* and *Euphorbia* respectively.
Preparation of doses—Declofenac and the dried ether extracts of both plants were suspended separately in water using 2% tylose as suspending agent. The vehicle which is 2% tylose in distilled water was given to rats of control group.

Design of experimental work—Rats were divided into 4 groups of 6 rats each. Rats in the first and second groups (test groups) were given ether extracts (500 mg/kg body wt) of E. peplus and R. graveolens respectively as daily oral dose. Rats in third group (reference group) were given daily oral dose (15 mg/kg body wt) of declofenac. An additional group was used as control where rats were given only the vehicle. The experiment continued for three weeks, during which rats were fed balanced diet. During the experimental period body weight and food intake were recorded twice weekly. At the end of the experiment, body weight gain, total food intake, food efficiency ratio (body weight gain/total food intake) and protein efficiency ratio (body weight gain/total protein intake) were calculated. Rats were fasted for 16 hr and blood was obtained from the vein orbital for the determination of haemoglobin and haematocrit. Sera were separated for the determination of serum total protein, albumin, iron and aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase activity, blood urea nitrogen and serum creatinine. Serum globulin values were obtained by subtracting serum albumin from serum total protein value. Albumin:globulin ratio (A/G) was calculated. Mean corpuscular haemoglobin concentration (MCHC) was calculated according to Nægeli. The data were statistically analyzed using Student’s t test.

Results and Discussion

The nutritional parameters (Table 1) showed that the final body weight, body weight gain and food efficiency ratio increased significantly \( (P < 0.05) \) on administration of the ether extract of R. graveolens. The increase in body weight was due to increase in total food intake, which may reflect an appetite stimulant effect of this extract. None of the nutritional parameters showed any significant changes on administration of Euphorbia extract or declofenac. Other non-steroidal anti-inflammatory drugs such as aspirin and indomethacin have been shown to produce reduction and no changes in protein efficiency ratio respectively. Methyl prednisolone, the steroidal anti-inflammatory drug, has been reported to severely reduce protein efficiency ratio. The growth curves of rats (Fig. 1) receiving E. peplus extract or declofenac did not show any significant changes compared to control rats. However, body weights of rats given R. graveolens started to increase on the tenth day and continued till the end of the experiment.

Serum total protein, albumin and globulin (Table 2) did not show any significant changes on administration of either R. graveolens or E. peplus ether extracts, however A/G ratio decreased significantly on administration of E. peplus. Administration of declofenac produced significant decrease of serum albumin.

![Fig. 1 — Effect of R. graveolens and E. peplus on growth curves of rats \( (P < 0.05) \)](image-url)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body wt (g)</th>
<th>Final body wt (g)</th>
<th>Body wt gain (g)</th>
<th>Total food intake (g)</th>
<th>Total protein intake (g)</th>
<th>Food efficiency ratio</th>
<th>Protein efficiency ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>50.5 ± 2.870</td>
<td>88.2 ± 4.510</td>
<td>38.2 ± 3.620</td>
<td>180 ± 10.500</td>
<td>18 ± 1.050</td>
<td>0.209 ± 0.033</td>
<td>2.19 ± 0.133</td>
</tr>
<tr>
<td>R. graveolens</td>
<td>51.3 ± 2.090</td>
<td>104 ± 4.060*</td>
<td>53 ± 3.088*</td>
<td>211 ± 13.400</td>
<td>21.1 ± 1.340</td>
<td>0.254 ± 0.015</td>
<td>2.54 ± 0.152*</td>
</tr>
<tr>
<td>E. peplus</td>
<td>50.5 ± 2.570</td>
<td>83.7 ± 4.530</td>
<td>33.2 ± 5.080</td>
<td>170 ± 16.500</td>
<td>17.0 ± 1.650</td>
<td>0.190 ± 0.020</td>
<td>1.90 ± 0.201</td>
</tr>
<tr>
<td>Declofenac</td>
<td>51.3 ± 1.930</td>
<td>90.3 ± 3.830</td>
<td>39 ± 3.910</td>
<td>182 ± 8.170</td>
<td>18.2 ± 0.815</td>
<td>0.215 ± 0.021</td>
<td>2.15 ± 0.213</td>
</tr>
</tbody>
</table>

*body wt gain/total food intake, †body wt gain/total protein intake \( *P < 0.05 \)
Indomethacin and methyl prednisolone were reported to produce significant reduction of serum total protein in growing rats while serum albumin was reduced only on administration of methyl prednisolone. Also, methyl prednisolone was reported to produce reduction in serum protein in rheumatoid arthritis in human. Concerning iron status, the present results (Table 2) showed non-significant changes in blood haemoglobin, haematocrit, serum iron and MCHC%. Methotrexate therapy in patients suffering rheumatoid arthritis has been reported to produce reduction in blood haemoglobin. Oral administration of indomethacin has been shown to produce non-significant changes in haemoglobin and haematocrit in growing rats.

No harmful effect was noticed in either liver or kidney function tests (Table 2) during administration of the ether extracts of the two plants or declofenac. Only significant elevation of alkaline phosphatase was noticed during treatment with ether extract of R. graveolens. Saraf and Dixit have reported safety and antihepatotoxic activity of water insoluble fractions of certain Euphorbia species. Methyl prednisolone therapy in rheumatoid arthritis produced elevation in alanin amino transferase and blood urea nitrogen.

Oral administration of methyl prednisolone produced significant elevation of serum ALT and no changes in AST and alkaline phosphatase or creatinine in adult rats.

From the results of the present study, it can be concluded that ether extracts of both E. peplus and R. graveolens are safe to be used as remedy except concerning the alkaline phosphatase elevating effect of R. graveolens. R. graveolens can improve the appetite, which is considered as a beneficial effect in chronic inflammatory diseases. Neither of the extracts produced any harmful effects on biochemical indices of nutritional status and kidney function. However, E. peplus was superior concerning safety towards liver function.

References

1. Daveve S A. Biologically active diterpene esters from Euphorbia peplus, Bull Sci Pharmacol, 15 (1908) 44.