Communications to the editors

ANTITUMOR ACTIVITY OF MONOGLYCERIDES AND OTHER ESTERS OF FATTY ACIDS

Sir:

Antitumor active monoglycerides have been isolated from the acetone extracts of the mycelia of *Sepedonium ampullosporum*<sup>1</sup>, *Cercospora oryzae*<sup>2</sup> and *Coriolus unicolor*<sup>3</sup>. Fatty acids composition of the monoglycerides was examined and it was found that hexadecanoic, octadecenoic and octadecadienoic acids are the main components<sup>4</sup>. They also contain other fatty acids as the minor components.

In order to determine the active principle in the mixtures of the monoglycerides, antitumor activity in vivo of each monoglycerides was studied using Ehrlich ascites tumor in mice. In addition to the monoglycerides, the glycerol esters of fatty acids, other esters were examined for the activity. In this paper we report the antitumor activity of monoglycerides and other esters of fatty acids.

In this study we chose those fatty acids with even carbon numbers between ten and eighteen. For the alcoholic moieties we selected methanol, propylene glycol, sorbitol and sucrose in addition to glycerol.

A part of the monoglycerides and all the sucrose esters were synthesized in this laboratory. Monoglycerides were synthesized according to the method of Daubert and Baldwin<sup>4</sup> except that pyridine was used instead of quinoline in the reaction mixture. For the synthesis of sucrose esters of fatty acids the method of Osrow et al.<sup>5</sup> was applied. Other materials were commercially available.

To examine purity of the fatty acid component of the esters each sample was subjected to methanolysis and the methyl esters obtained were analyzed with gas-

### Table 1. Antitumor activity of monoglycerides

<table>
<thead>
<tr>
<th>Monoglycerides</th>
<th>Dose (mg/mouse/day)</th>
<th>7 Days after implant</th>
<th>Survival time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor</td>
<td>Body wt. gain (g)</td>
<td></td>
</tr>
<tr>
<td>Monostearin</td>
<td>10.0</td>
<td>++ + + +</td>
<td>+4.0 +5.3</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>+ + + + +</td>
<td>+2.3 +2.9</td>
</tr>
<tr>
<td>Monoolein</td>
<td>6.0</td>
<td>+ + + + +</td>
<td>+7.0 +7.8</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>+ + + + + +</td>
<td>+7.0 +7.8</td>
</tr>
<tr>
<td>Monolinolein</td>
<td>6.0</td>
<td>+ + + + + +</td>
<td>+7.0 +7.8</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>+ + + + + +</td>
<td>+7.0 +7.8</td>
</tr>
<tr>
<td>Monolinolenin</td>
<td>20.0</td>
<td>+ + + + + +</td>
<td>+6.8 +3.6</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>+ + + + + +</td>
<td>+6.0 +3.1</td>
</tr>
<tr>
<td>Monopalmitin</td>
<td>10.0</td>
<td>+ + + + + +</td>
<td>+4.7 +5.0</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>+ + + + + +</td>
<td>+2.8 +1.6</td>
</tr>
<tr>
<td>Monomyristin</td>
<td>10.0</td>
<td>+ + + + + +</td>
<td>+4.2 +2.5</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>+ + + + + +</td>
<td>+5.3 +7.5</td>
</tr>
<tr>
<td>Monolaurin</td>
<td>10.0</td>
<td>+ + + + + +</td>
<td>+2.1 +0.5</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>+ + + + + +</td>
<td>+3.7 +4.4</td>
</tr>
<tr>
<td>Monocaprin</td>
<td>20.0</td>
<td>+ + + + + +</td>
<td>+0.6 +1.9</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>+ + + + + +</td>
<td>+0.6 +1.9</td>
</tr>
<tr>
<td>Monocaproin</td>
<td>10.0</td>
<td>+ + + + + +</td>
<td>+2.0 +5.2</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>+ + + + + +</td>
<td>+7.5 +7.3</td>
</tr>
<tr>
<td>Control</td>
<td>0.0</td>
<td>+ + + + + +</td>
<td>+8.8 +9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ + + + + +</td>
<td>+9.5 +6.4</td>
</tr>
</tbody>
</table>

The method of the assay is described in the text. Two mice were used for each dose in this experiment. The degree of the tumor growth is as follows: +++ marked growth, ++ moderate growth, + slight growth, − no growth.
liquid chromatography using a poly butane-
diol succinate column. The results indicated
that all of the samples were 70\% \textendash}90 \% pure
for fatty acid components.

Antitumor activity in vivo was assayed
using \textsc{Ehrlich} ascites tumor in mice. The
ascitic tumor cells of \textsc{Ehrlich} carcinoma
\((2\times10^6 \text{ cells})\) were implanted intraperito-
neally in \textit{ddY} mice, 5 weeks old, weighing
18 to 22 g. Saline solution of the samples
was administered once daily for 5 successive
days and the tumor growth and body
weight gain after 7 days and life span were
observed.

Antitumor activity of nine monoglycerides
is shown in Table 1. When the tumor
growth after 7 days was compared with
that of the control mice, stearic, linoleic
and caproic monoglycerides were thoroughly
ineffective, whereas linolenic, oleic, palmitic,
myristic and capric glycerides were some-
what effective and monolaurin completely
inhibited the tumor growth at two doses
tested. Most of the treated animals showed
prolongation of the survival period while
control mice were observed to die within 17
days. In the cases of monolinolenin, mono-
olein and monopalmitin some of the mice
survived more than 30 days but their tumor
cure was not complete. On the other hand,
monomyristin- and monolaurin-treated mice
exhibited complete cure though their sur-
vival periods were more or less short.
Thus, monoglycerides with carbon numbers
between 12 and 16 were active against
\textsc{Ehrlich} ascites tumors in mice. Moreover
some of the unsaturated monoglycerides with
18 carbon atoms in their fatty acids, namely
monooolein and monolinolenin, were also
active in vivo.

When the antitumor activity of sucrose es-
ters of linoleic, palmitic, myristic, lauric and
capric acids was examined, palmitic, myristic
and lauric esters exerted remarkable inhibi-
tion of the tumor growth with prolongation
of the survival time. In the case of pro-
pylene glycol esters, oleic, palmitic and
myristic esters were examined and myristic
ester showed a complete cure with prolonged
survival time. All of the methyl esters and
sorbitol esters tested were inactive against
the tumor except methyl laurate which
exerted an inhibitory activity against the
tumor.

The details of this study will be reported
elsewhere.

Acknowledgement

We wish to thank Taiyo Kagaku Kogyo Co.,
Ltd. for some of the monoglycerides and propylene
glycol and sorbitol esters of fatty acids.

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