Effects of Japanese Kelp (Kombu) on Life Span of Benzo[a]pyrene-Fed Mice

Hiroyuki SAKAKIBARA1, Satoshi NAKAGAWA2, Hiroko WAKAMEDA3, Yoshiko NAKAGIRI2, Kimiko KAMATA1, Swadesh K. DAS1, Takahiko TSUJI3 and Kazuki KANAZAWA2,*

1 Department of Life Science, Graduate School of Science and Technology and 2 Faculty of Agriculture, Kobe University, Rokkodai, Nada-ku, Kobe 657–8501, Japan
3 Oguraya Yamamoto Food Co., Ltd., Minamisenba 4–7–21, Chuo-ku, Osaka 542–0081, Japan

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Summary The prolonging effect of Japanese kelp (kombu) on life span was investigated in mice fed a diet containing the carcinogen benzo[a]pyrene (BaP). Three groups of six mice each were fed a normal diet with 0, 2 and 5% kombu powder, while another three groups were fed those diets with 4 ppm BaP loading. The 2 and 5% kombu diets did not affect life span compared to the control group given 0% kombu. BaP significantly reduced the life span. Addition of 2 or 5% kombu to the BaP diet remarkably recovered the life span to a level similar to that of the control. The feces of the 2 and 5% kombu groups contained 6.9±1.2 and 16.8±1.8% of the ingested BaP, respectively, mainly in forms adsorbed on kombu fibers. The BaP-alone group given cellulose as dietary fiber instead of kombu, did not show any such effects. Humans are exposed to various environmental carcinogens such as BaP, and kombu fibers probably contribute to longevity by removing them.

Key Words kombu, benzo[a]pyrene, longevity, dietary fibers, removal of dietary carcinogen

Japanese kelp (Laminaria japonica Areschoug), namely kombu, is a brown sea alga, the consumption of which is around 150,000 ton per year by fresh weight. The Japanese have traditionally used kombu in auspicious ceremonies believing it to increase longevity. In Okinawa, in southernmost Japan, the people traditionally eat a large amount of kombu, and have been reported to have the longest life span in Japan (1, 2). Therefore, we are interested in obtaining evidence of a longevity effect.

Kombu includes various beneficial ingredients for our health. One of the polysaccharides, fucoidan, is known to prevent tumors through immunopotential activity (3, 4). The micronutrients, iodine (5), β-carotene and fucoxanthin (6), and β-glucan (7) are reported to have anticarcinogenic activity. The longevity effect of kombu on Okinawans is assumed to be associated with preventive activity against cancer risk, because cancer is one of the most degenerative diseases that reduces the life span.

In the present study, one of the most abundant environmental carcinogens, benzo[a]pyrene (BaP) (8), was employed, and mice were fed on 4 ppm BaP loaded diets. BaP has been reported to induce cancer at a concentration of 200 μg/kg of body weight/d after 300 d in 50% of mice (9–11). The 4-ppm BaP diet corresponds to 200 μg BaP/kg of body weight/d, based on the daily consumption of diets by mice (4.0 g/d). Kombu was examined for longevity effects in mice.

*MATERIALS AND METHODS

Animals and diets. Animal treatments in this study conformed to all the “Guidelines for the care and use of experimental animals, Rokkodai Campus, Kobe University.” Male CDF1 mice aged 7 wk (initial body weight, 22–25 g; Japan SLC, Shizuoka, Japan) were housed in chop-sheeted plastic cages in a temperature-controlled (25±4°C) room with 60±5% humidity and a 12-h light-dark cycle. A total of 36 mice were equally divided into six groups: normal diet, normal+2% kombu, normal+5% kombu, BaP diet, BaP+2% kombu, and BaP+5% kombu as shown in Table 1, and each group was housed in a single cage. The diets (4 kg each) were prepared every 3 mo with cornstarch, casein, dextrinized cornstarch, soybean oil, cellulose powder, L-cystein, choline bitartrate, and tert-butylhydroquinone (Nacalai Tesque, Kyoto, Japan), AIN-93 vitamin mix and mineral mix (ICN Biomedicals, Inc., Aurora, OH), and sucrose, followed by storage at 4°C. Soybean oil was freshly supplemented every week to avoid autoxidation. BaP (Nacalai Tesque) was dissolved in soybean oil at a concentration of 2.0 mg/20 g.

Kombu (commercial name: Osatsube), which was harvested and dried in Hakodate (Hokkaido, Japan), was powdered into less than 90 μm with mesh. The kombu powder used here was analyzed for macro-ingredients at the Japan Food Research Laboratories (Tokyo, Japan). The powder included dietary fiber, mainly alginic acid, at 31.9% by dry weight when determined by the Prosky method (12), and carbohydrates at 39.1% by dry weight (Table 2). According to
Table 1. Diet composition.

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>2% Kombu</th>
<th>5% Kombu</th>
<th>BaP</th>
<th>BaP+2% kombu</th>
<th>BaP+5% kombu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal diet&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3,570</td>
<td>3,570</td>
<td>3,570</td>
<td>3,570</td>
<td>3,570</td>
<td>3,570</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BaP-containing soybean oil&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>160</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>Cellulose</td>
<td>200</td>
<td>175</td>
<td>135</td>
<td>200</td>
<td>175</td>
<td>135</td>
</tr>
<tr>
<td>Kombu powder&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0</td>
<td>80</td>
<td>200</td>
<td>0</td>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td>Additional cornstarch</td>
<td>70</td>
<td>40</td>
<td>0</td>
<td>70</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup> The basal diet consisted of 1,794 g cornstarch, 560 g casein, 620 g dextrinized cornstarch, 400 g sucrose, 40 g AIN-93 vitamin mix (13), 140 g AIN-93 mineral mix (13), 7.2 g L-cystein, 10 g choline bitartrate, and 0.032 g tert-butylhydroquinone.

<sup>2</sup> 16 mg BaP was dissolved in 160 g of soybean oil.

<sup>3</sup> The kombu powder contained 31.9% dietary fibers and 39.1% polysaccharides as shown in Table 2.

Table 2. Ingredients of kombu.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Composition (per g kombu powder)</th>
<th>Determination with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary fibers</td>
<td>319 mg</td>
<td>Prosky method (12)</td>
</tr>
<tr>
<td>Proteins</td>
<td>70.6 mg</td>
<td>Kjeldahl method as N×6.25</td>
</tr>
<tr>
<td>Lipids</td>
<td>18.5 mg</td>
<td>Folch partition method</td>
</tr>
<tr>
<td>Ashes</td>
<td>149 mg</td>
<td>Direct burning method at 550°C</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>391 mg</td>
<td>1,000 mg–others&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Water</td>
<td>51.0 mg</td>
<td>Drying up method at 110°C</td>
</tr>
</tbody>
</table>

<sup>4</sup> Carbohydrate amount was estimated by deducting amounts of all of the other ingredients from 1 g.

The diet composition for laboratory rodents in AIN-93 (13), the dietary fiber composition was raised to 5% with the addition of cellulose, and the starch to 46.6% with cornstarch (Table 1). Soybean oil, cellulose, additional cornstarch, and kombu powder were mixed with the basal diet. The diets and water were renewed every day, and the animals were given free access to both. The body weights were measured every week.

**BaP in feces.** Feces were collected, dried and weighed. BaP was extracted from 5 g of feces with 10 mL of ethyl acetate three times, and was referred to as free BaP. The residues after extraction were hydrolyzed with 2 N HCl at 40°C for 2 h and extracted again, being referred to as adsorbed BaP in dietary fibers. Both extracts were dried under a nitrogen stream and dissolved in 200 μL of dimethylsulfoxide (DMSO). After filtration with a 0.2 μm membrane filter Millex-LG (Millipore Co., Bedford, USA), BaP and its oxides were determined using HPLC by a modified method of McElroy et al. (14) as follows: column, Wakosil-II 5C18AR 4.6×200 mm (Wako Pure Chemical Industries, Ltd., Tokyo, Japan) maintained at 35°C; mobile phase, 95% methanol and 5% water containing 0.1% acetic acid; flow rate, 1.0 mL/min; detection, 260 nm using a HITACHI detector, model No. L-7420 (Tokyo, Japan).

**Data analysis.** The data for life span and body and organ weights were analyzed with two-way ANOVA followed by a Fisher’s PLSD post-hoc test with StatView software (Abacus Concepts, Berkeley, CA). The difference was considered significant at p<0.05.

**RESULTS**

**Prolonging effects on life span**

The six groups of mice showed unremarkable body weight gain until they died. The mice of the 5% kombu group were playful and more active as compared with those of the control group. Table 3 shows food consumption at ages from 200 to 250 d and from 400 to 510 d. For the first age term the 2% kombu and BaP+5% kombu groups made significantly higher gain in weight than the other groups, but the food consumptions were similar to each other. This was possibly because they were not so playful. The BaP group for the second age term made lower gains in weight despite the significantly higher food consumptions, suggesting that BaP exerted a harmful effect. Table 4 shows the body, organ and tissue weights. For most organs, weights were similar among the groups. The spleen weights were lower in the kombu group compared to the control. The BaP and BaP+5% kombu groups had higher testis weights than the others.

The mice of the BaP-alone group became acutely lethargic a few days before they died. Their organs had darkened in color when dissected within 6 h of death.
Table 3. Body weights and diet consumptions at the surviving term of animals.  

<table>
<thead>
<tr>
<th>Group</th>
<th>Age of 200–250 d</th>
<th></th>
<th>Age of 400–510 d</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body weight (g)</td>
<td>Consumed diet (g/mouse/d)</td>
<td>Body weight (g)</td>
<td>Consumed diet (g/mouse/d)</td>
</tr>
<tr>
<td>Control</td>
<td>36.3±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.9±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35.0±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.3±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2% Kombu</td>
<td>41.6±0.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.0±1.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>34.6±0.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.7±1.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5% Kombu</td>
<td>35.9±0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.9±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.5±1.0&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.5±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BaP</td>
<td>36.4±1.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1±0.9&lt;sup)a&lt;/sup&gt;</td>
<td>33.6±1.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.3±0.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BaP+2% kombu</td>
<td>35.7±0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0±1.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.5±1.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.7±1.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BaP+5% kombu</td>
<td>38.6±0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0±0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.3±0.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.6±0.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1 Body weights are the means±SD (n=6); those with a different superscript are significantly different at p<0.05.
2 The consumed amounts of diet in each cage per day were divided by the number of mice. The values are mean±SD of everyday, 51 or 111 d, and in each column a different superscript indicates a significant difference at p<0.05.

Table 4. Body and tissue weights of the dead mice.

<table>
<thead>
<tr>
<th>Group</th>
<th>Body</th>
<th>Liver</th>
<th>Kidney</th>
<th>Heart</th>
<th>Spleen</th>
<th>Testis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28.5±3.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.21±0.37&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.63±0.14&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>0.19±0.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.21±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2% Kombu</td>
<td>28.6±2.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.24±0.28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.54±0.10&lt;sup&gt;b,abc&lt;/sup&gt;</td>
<td>0.28±0.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.11±0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.09±0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5% Kombu</td>
<td>28.1±3.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.52±0.56&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.47±0.09&lt;sup&gt;b,abc&lt;/sup&gt;</td>
<td>0.21±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.11±0.04&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.12±0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BaP</td>
<td>29.4±4.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.42±0.16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.58±0.14&lt;sup&gt;b,abc&lt;/sup&gt;</td>
<td>0.24±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.14±0.07&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.17±0.04&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BaP+2% kombu</td>
<td>28.0±5.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.36±0.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.44±0.19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.29±0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10±0.06&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BaP+5% kombu</td>
<td>28.4±5.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.32±0.67&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.66±0.20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.29±0.15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.13±0.10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.18±0.05&lt;sup&gt;b,abc&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1 These weights were measured immediately after the animals died on the day shown in Fig. 2. Values are the means±SD (n=6); those with a different superscript are significantly different at p<0.05.

Fig. 1. Effects of kombu on average life spans of BaP-fed mice. Values are the mean±SD (n=6), and different letters indicate a significant difference at p<0.05.

Lungs, liver, and intestines showed septicemia-like petechiae, and the lung especially was in severe necrotic condition. However, no tumors were found under optical observation. In the other groups including the BaP with kombu groups, such an indication was not observed and no other hyperplasia lesions were detected.

The average life spans were analyzed statistically (Fig. 1). The life spans of the 2% and 5% kombu groups were 746±183 and 851±225 d as the mean±SD (n=6), respectively, and were similar to the 907±135 d of the control group without kombu, indicating that the kombu did not affect the life spans. Four-ppm BaP in the diet significantly reduced the life span to 616±151 d compared to that in the control. The addition of 2% kombu to the BaP diet significantly recovered the life span to a level similar to that of the control, 837±103 d. The addition of 5% kombu also recovered the life span to 760±222 d (not significantly). The survival curves are shown in Fig. 2. The life span in the control group ranged from 728 to 1,084 d. In the BaP group, the mice died during days 419–682 except for one mouse which lived for 864 d. In the BaP group, the mice died during days 419–682 except for one mouse which lived for 864 d. Mice of the BaP+2% kombu group lived for 703–956 d. In the BaP+5% group, two mice died on days 508 and 527 and the others survived for 787–1,109 d. A visual inspection of the survival curves suggested that the BaP-alone group had a shorter life span than the control. Comparing the days mealing the survival of only three animals, the 50% survival ages were remarkably recovered in the BaP+2% kombu and BaP+5% kombu groups to levels similar to that of the control (Fig. 2). The results indicated that both 2% and 5% kombu in the diet detoxified BaP and thereby maintained the original life span.

Adsorption of BaP by kombu

The longevity effect of kombu is mainly contributed
Fig. 2. Effects of kombu on survival of BaP-fed mice.

Table 5. Fecal excretion of ingested BaP.

<table>
<thead>
<tr>
<th>Group</th>
<th>Free BaP</th>
<th>Adsorbed BaPs in dietary fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BaP</td>
</tr>
<tr>
<td>Control</td>
<td>not detected</td>
<td>not detected</td>
</tr>
<tr>
<td>BaP</td>
<td>2.12±0.42a</td>
<td>1.70±0.34a</td>
</tr>
<tr>
<td>BaP+2% kombu</td>
<td>0.566±0.088b</td>
<td>2.57±0.34b</td>
</tr>
<tr>
<td>BaP+5% kombu</td>
<td>0.105±0.013c</td>
<td>29.6±2.6c</td>
</tr>
</tbody>
</table>

1 Mouse feces were recovered every week at the ages of 200 to 250 d, and analyzed independently. Values are the mean±SD (n=6). In each column, a different superscript indicates a significant difference at p<0.05.
2 See Table 1 for the mouse groups.
3 Free BaP was extracted from feces with ethyl acetate and determined by HPLC as described in Materials and Methods.
4 The residues after extraction were treated in 2 N HCl and extracted again, and then analyzed by HPLC as described in Materials and Methods.
5 By HPLC, several peaks for oxidized BaP were detected, mostly 7-hydroxyl BaP and minor forms, 7,8-diol and 1,6 or 3,6-diols. The oxidized BaPs were determined with absorbance of BaP at 260 nm and summed.

DISCUSSION

The present results demonstrate that kombu prolongs the life span of mice fed BaP. Humans are exposed to various carcinogens such as BaP (9-11) and heterocyclic amines (16, 17) produced during cooking and liberated from exhaust gas. These are activated in the body to the ultimate carcinogenic forms via a metabolic mechanism by cytochrome P450 1A monooxygenases (18-21). Thus, humans are considered to be under similar conditions of BaP contamination as tested in the present study. Mice given the diet containing 4 ppm BaP diet, 0.34 g for the BaP+2% kombu and 0.25 g for the BaP+5% kombu group. When the sum total of detected BaPs was calculated with diet consumption in Table 3, the BaP-alone group excreted 3.5±0.42% of ingested BaP into the feces; the values for the BaP+2% kombu and BaP+5% kombu groups were 6.9±1.2 and 16.8±1.8%, respectively. The BaP-alone group was fed cellulose instead of kombu dietary fibers as shown in Table 1. The results revealed that high fecal excretion of BaP was characteristic of kombu dietary fibers.

The results of this study suggest that kombu may be effective in reducing the risk of cancer in humans who are exposed to BaP-containing substances. Further research is needed to investigate the mechanisms by which kombu enhances the detoxification of BaP in the body.
grew just as the control did but their life span was sig-
ificantly shorter than that of the control (Figs. 1 and
2). The addition of dietary kombu at 2 and 5% did not
affect the original life span of control mice, but 2 or 5%
kombu powder added to the BaP diet improved the life
span to the same level as in the control without BaP.
Thus, the dietary kombu powder served as a preventive
against environmental carcinogen in mice. The kombu
intake can be calculated to be 20 and 50 g per day for a
person who consumes about 1 kg of food daily.

The effect of kombu on longevity is probably involved
in inhibition of the absorption of BaP into the body. The
BaP plus 2 or 5% kombu group excreted 6.9 or 16.8%
of the ingested BaP into the feces, respectively, and the
BaP-alone group given cellulose instead of kombu
excreted 3.5% of the ingested BaP (Table 5). Taken alto-
gether, it seems likely that kombu dietary fiber adsorbs
BaP in preference to the others, elevates its fecal excre-
tion and brings about elongation of the life span. The
preventive effect of kombu intake against carcinogene-
sis warrants further investigation from the standpoint
of experiment with an animal model as well as its epide-
miology in people.

Acknowledgments
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Funds of the Ministry of Education, Culture, Sports, Sci-
ence and Technology, the Japanese Government.

REFERENCES
1) Sho H. 2001. History and characteristics of Okinawan
2) Taira K, Tanaka H, Arakawa M, Nagahama N, Uza M,
Shirakawa S. 2002. Sleep health and lifestyle of elderly
people in Oqimi, a village of longevity. Psychiatry Clin
Neurosci 56: 243–244.
1993. Antitumor activity and immunological proper-
ties of marine algal polysaccharides, especially fucoidan,
prepared from Sargassum thunbergii of Phaeophyceae.
4) Maruyama H, Tamauchi H, Hashimoto M, Nakano T.
2003. Antitumor activity and immune response of
Mekabu fucoidan extracted from Sporphyll of Undaria
5) Funahashi H, Imai T, Tanaka Y, Tsukamura K, Hayakawa
Y, Kikkumi T, Mase T, Itoh T, Nishikawa M, Hayashi H,
Wakame seaweed suppresses the proliferation of
7,12-dimethylbenz(a)-anthravene-induced mammary
6) Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, Baba-
Toriyama H, Ota T, Nir Z, Khachik E, Shimidzu N,
Tanaka Y, Osawa T, Uraji T, Murakoshi M, Nishino H,
Tsudo H. 1998. Chemopreventive effects of carotenoids
and curcumins on mouse colon carcinogenesis after
1,2-dimethylhydrazine initiation. Carcinogenesis 19:
81–85.
7) Teas J. 1983. The dietary intake of Laminaria, a brown
seaweed, and breast cancer prevention. Nutr Cancer 4:
217–222.
carcinogens. In: Naturally Occurring Carcinogens-
Mutagens and Modulators of Carcinogenesis (Miller
Ec, Miller JA, Hirono I, Sugimura T, Takayama S,
10) Albert RE, Miller ML, Cody T, Andringa A, Shukla R,
and tumor promotion in the mouse. Carcinogenesis 12:
1273–1280.
K, Kamataki T. 1999. Inhibition of benzo[a]pyrene-
induced mutagenesis by (−)-epigallocatechin gallate in
the lung of rpdL transgenic mice. Carcinogenesis 20:
421–424.
12) Prosky L. 1990. Collaborative study of a method for sol-
uble and insoluble dietary fiber. Adv Exp Med Biol 270:
193–203.
purified diets for laboratory rodents: final report of the
American Institute of Nutrition Ad Hoc Writing Com-
mittee on the reformulation of the AIN-76 rodent diet. J
benzo[a]pyrene metabolism in small benthic marine
15) Jack P, Brookes P. 1980. The binding of benzo(a)pyrene
to DNA components of differing sequence complexity.
Food-derived mutagens and carcinogens. Cancer Res 52:
2092–2098.
Organ-specific distribution of genotoxic effects in mice
exposed to cooked food mutagens. Mutagenesis 7:
In: Handbook of Experimental Pharmacology (Schenk-
man JB, Greim H, eds), p 221–238. Springer-Verlag,
Berlin.
19) Minamoto S, Kanazawa K. 1995. Electrochemical deter-
mination for enzymic production of ultimate carcinoegen
from tryptophan pyrolysate by rat hepatic microsomes.
20) Butcher NJ, Minchin RF, Kadlubar FF, Ilett KF. 1996.
Uptake of the food-derived heterocyclic amine carcinoegen
2-amino-1-methyl-6-phenylimidazo[4,5-]pyridine and
its N-hydroxy metabolite into rat pancreatic acini and
21) Boyd GW, Young RJ, Harvey RG, Coombs MM, Ioan-
nides C. 1993. Cytochrome P450-dependent metabo-
lism and mutagenicity of 15,16-dihydro-11-methylcy-
clopetenta[alphabeton]thranthren-17-one and their impli-
cations in its carcinogenicity. Carcinogenesis 14:
1783–1788.