CARCINOGENIC ACTIVITY OF COLTSFOOT, *Tussilago farfara* L.*1

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The carcinogenicity of young, pre-blooming flowers of coltsfoot, *Tussilago farfara* L., which is a herb of the tribe Senecioneae, family Compositae, and widely used as a herbal remedy, was studied in inbred strain ACI rats. Rats were divided into 4 groups: Group I received 32% coltsfoot diet for 4 days, and subsequently 16% diet until the termination of experiment. Groups II and III respectively received 8% and 4% coltsfoot diet for 600 days. Group IV was fed a normal diet as a control group. The experiments were terminated 600 days after the start of administration of coltsfoot diet. All the rats in Group I survived beyond 380 days after the start of feeding and 8 out of 12 rats developed hemangioendothelial sarcoma in the liver, whereas only one out of 10 rats developed the tumor in Group II, and no tumors were observed in Group III. Chemical studies on the dried, young flowers used in this experiment suggested that the carcinogenicity of coltsfoot is most probably due to senkirkine, a hepatotoxic pyrrolizidine alkaloid.

We have reported previously the carcinogenic activity of young flower stalks of *Petasites japonicus* Maxim., a kind of coltsfoot.*3,5) In the present study, the carcinogenicity of young, pre-blooming flowers of coltsfoot, *Tussilago farfara* L., which is a herb of the tribe Senecioneae, family Compositae, and widely used as a herbal remedy in Japan, was investigated in inbred strain ACI rats.

Materials and Methods

The dried, pre-blooming flowers of coltsfoot known as “Kan-to-ka” in Japanese and which are imported into Japan as a herbal drug from China (Photo 1), were milled and mixed with the rat basal diet CE-2 (CLEA Japan Inc., Tokyo) at various ratios. The composition of the basal diet CE-2 was described elsewhere.4) Rats of both sexes, 1.5 months old, were divided into 4 groups as follows:

- **Group I**: Six male and 6 female rats received 32% coltsfoot diet for 4 days. Subsequently, the concentration of the coltsfoot in the diet had to be reduced to 16% because the animals in this group were reluctant to eat the diet and they lost weight. They were fed the 16% coltsfoot diet until termination of the experiment.
- **Group II**: Five male and 5 female rats received 8% coltsfoot diet for 600 days.
- **Group III**: Six male and 5 female rats received 4% coltsfoot diet for 600 days.
- **Group IV**: Eight males and 8 females served as controls and were fed the normal diet without coltsfoot material.

Water was given freely. The experiments were terminated 600 days after the start of administra-
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All the animals were autopsied at death or when killed due to moribund condition or termination of the experiment. Tissues were fixed in 10% Formalin, sectioned, and stained with Hematoxylin and Eosin.

Results

All the animals in Group I survived beyond 380 days after the start of the experiment. Eight out of 12 rats, 5 males and 3 females, developed hemangioendothelial sarcoma in the liver (Table I). These hemangioendothelial sarcomas were induced only in the liver as relatively soft and hemorrhagic nodules. Microscopically, the tumor was composed of plump irregular cells forming vascular spaces and there were some areas of hemorrhage (Photo 2). The tumor was multicentric in some cases. Metastatic spread of the tumor was observed in the lung in 4 animals and in the adrenal in one animal. In addition, 3 of 8 rats which had hemangioendothelial sarcoma developed simultaneously hepatocellular adenoma, hepatocellular carcinoma, or urinary bladder papilloma. In Group II animals given 8% coltsfoot diet, all the animals survived beyond 420 days except one rat which was sacrificed due to moribund condition 282 days after the start of experiment. Only one rat developed hemangioendothelial sarcoma in the liver. In Group III animals that received 4% coltsfoot diet, all the animals survived beyond 445 days after the start of feeding, and no tumors were observed.

Discussion

The liver tumors observed in this experiment were not encountered in any of the control rats nor in another group of about 150 rats serving as controls in previous long-term experiments. Based on these results, it is evident that the young, pre-blooming flowers of coltsfoot are carcinogenic, showing a high incidence of hemangioendothelial sarcoma of the liver (8/12, 66.6%). Histological changes in the liver, such as centrilobular necrosis of liver cells, peliosis hepatis, proliferation of the intrahepatic bile duct, or liver cirrhosis were frequently encountered even in rats in experimental groups which had no tumors. These histological findings of the liver strongly suggested that the coltsfoot may contain a hepatotoxic pyrrolizidine alkaloid.1,6

Chemical studies on the dried, milled young flowers used in this experiment revealed that the pyrrolizidine alkaloid was present in a low concentration (0.015%) and that the only constituent detectable by gas chromatography-mass spectrometry was.

| Time after initiation of feeding (months) | Group I | | Group II |
|---|---|---|
| | No. of dead rats | No. of rats with hemangioendothelial sarcoma | No. of dead rats | No. of rats with hemangioendothelial sarcoma |
| ~10 | 1 | 1 |
| 12~13 | 1 | |
| 13~14 | 1 | |
| 14~15 | 2 | 1 |
| 15~16 | 2 | 2 |
| 16~17 | 1 | 1 |
| 17~18 | 1 | 1 |
| 18~19 | 2 | 2 |
| 19~20 | 2 | 3 |
| Total | 12 | 8 | 10 | 1 |

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* Hepatocellular adenoma was observed simultaneously.

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* Hepatocellular carcinoma was also observed in one of these two.
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Senkirkine has been found to be hepatotoxic by Schoental, and it is most probable that the carcinogenicity of coltsfoot is due to senkirkine. In a previous experiment, rats fed 4% diet of Petasites japonicus, which is a herb of the same botanical tribe as coltsfoot, produced a high incidence of hemangioendothelial sarcoma of the liver. In the case of coltsfoot, however, the tumor was induced only in rats which received the diet containing coltsfoot in a concentration higher than 4%. Such a difference in tumor incidence may be attributed to a difference in alkaloids or in alkaloid concentration. It is conceivable that coltsfoot material prepared by a different procedure may show more potent carcinogenicity. Pre-blooming flowers of coltsfoot are used as a cough cure or expectorant in Chinese medicine and popular European remedy. Therefore, it is noteworthy that such a herb drug shows a carcinogenic activity.

(Received September 26, 1975)

REFERENCES


EXPLANATION OF PLATE

Photo 1. Dried, pre-blooming flowers of coltsfoot, Tussilagofarfara L., used in this experiment.
Photo 2. Histological findings with hemangioendothelial sarcoma of the liver in Group I rat. × 360.
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