The most representative naturally occurring carcinogens of plant origin are pyrrolizidine alkaloids,\(^1,7,8\) cycasin,\(^6\) and bracken carcinogen.\(^3\) We have reported the carcinogenic activity of unprocessed young bracken\(^3\) and of processed bracken used as a human food.\(^4\) In Japan, especially in rural area, various kinds of wild plant have long been accepted as human food. Carcinogenicity examination of artemisia, horsetail, and osmund, which are popular edible wild plants, has already been carried out,\(^5\) but these plants had no carcinogenicity. In the present study, the carcinogenicity of young flower stalks of Petasites japonicus MAXIM. (Japanese name “Fuki-no-toh”), a kind of coltsfoot, which is bitter as bracken and has long been used as a food or a herbal remedy, such as a cough cure, expectorant, or stomachic, was investigated in inbred strain ACI rats.

**Materials and Methods**

The young flower stalk of Petasites japonicus was collected in Gifu Prefecture, in the nearly central part of Japan, from the end of March to April. It was in the edible stage of maturation (Photo 1). To prepare the coltsfoot diet, the fresh flower stalk was dried in a dryer equipped with a blower. This material was then milled, mixed with the rat basal diet CE-2 (CLEA Japan Inc., Tokyo) in 4 or 8% of the total. The composition of the basal diet CE-2 was described previously.\(^3\) The animals were divided into the following three groups: Group 1: For 6 months, 12 male and 15 female ACI rats, 1 month old, received the 4% coltsfoot diet. Subsequently, they received alternately 8% coltsfoot diet for 1 week and a coltsfoot-free normal diet for 1 week, until the experiment was terminated. Group 2: Until the termination of the experiment, 11 male and 8 female rats, 1 month old, received the 4% coltsfoot diet. Control group: A group of 7 males and 7 females served as controls; they were fed the normal diet. Water was given freely.

The experiments were terminated 480 days after the start of administration of coltsfoot diet. All the animals were autopsied at death or when killed due to moribund condition. Tissues were fixed in 10% Formalin, sectioned, and stained with Hematoxylin and Eosin.

**Results and Discussion**

Twenty-five of 27 rats in Group 1 survived beyond 430 days, except 1 female and 1 male rats which died of pneumonia 155 and 161 days after the start of experiment, respectively, and 3 rats developed hemangioendothelial sarcomas of the liver (Photos 2 and 3), 6 rats liver cell adenomas, and 2 rats hepatocellular carcinomas as shown in Table I. In Group 2, all the rats survived beyond 220 days after the start of experiment and 8 rats had hemangioendothelial sarcomas. Liver cell adenoma was induced in 4 rats and hepatocellular carcinoma in 1 rat. These tumors were not encountered in any of the control rats nor in another group.
of about 50 rats serving as controls in another long-term experiment. In this study, the hemangioendothelial sarcomas were induced only in the liver as relatively soft and hemorrhagic nodules (Photo 2). In most rats with hemangioendothelial sarcomas, the peritoneal cavity contained various amounts of free blood.

Microscopically, the tumor was composed of plump irregular cells forming a complex vascular network and there were some areas of hemorrhage. Mitoses of tumor cells were frequent, and in some cases the tumor was multicentric. Four out of the 11 animals with hemangioendothelial sarcoma in Groups 1 and 2 showed metastases in the lung (Photo 4) or perihepatic lymph nodes. The incidence of hemangioendothelial sarcoma in Group 2 was higher than in Group 1 (P<0.05), i.e., rats given 4% coltsfoot diet consecutively until the termination of experiment showed a higher incidence than those given 4% coltsfoot diet for 6 months and subsequently 8% coltsfoot diet intermittently. As to the sex of animals which had the hemangioendothelial sarcoma, 3 rats in Group 1 were males, and 6 were males and 2 females in Group 2. Thus, the sex difference in the incidence of hemangioendothelial sarcoma was not statistically significant in either group (p>0.05). From results obtained in this study, it may be evident that the flower stalk of *Petasites japonicus* is carcinogenic, showing a high incidence of hemangioendothelial sarcoma of the liver.

Studies on the nature of carcinogen contained in the flower stalks are now in progress.

We thank Dr. Y. Nishio, Gifu Prefectural Gero Hospital, for his kind supply of the plant material.

(Received May 26, 1973)

**REFERENCES**


**EXPLANATION OF PLATES**

LXXIII–LXXIV

Photo 1. Flower stalks of *Petasites japonicus* Maxim. The whole flower stalk seen in this photograph was used as the material.

Photo 2. Hemangioendothelial sarcoma of the liver in Group 1 rat, 480 days after the start of experiment. A hemorrhagic nodule measuring about 2.5 cm in diameter is seen.

Photo 3. Microscopical findings with hemangioendothelial sarcoma of the liver in Group 1 rat, 468 days after the start of experiment. Tumor cells form a complex vascular network. ×260.

Photo 4. Metastatic spread of hemangioendothelial sarcoma into the lung in Group 2 rat, 430 days after the start of experiment. ×260.