Toxicologia e carcinogenicidade da raiz Goldenseal – Hydrastis Canadensis (berberine) : não há


Toxicology and carcinogenesis studies of goldenseal root powder (Hydrastis Canadensis) in F344/N rats and B6C3F1 mice (feed studies).

Abstract

Goldenseal root powder is used in folk medicine for the treatment of gastrointestinal disturbances, urinary disorders, hemorrhage, skin, mouth, and eye infections, and inflammation. The major alkaloids in goldenseal are berberine, hydastine, and canadine. Goldenseal root powder was nominated for study by the National Institute of Environmental Health Sciences based on the potential for human exposure and the lack of carcinogenicity data, and because it is one of the most widely used herbs in the United States. Male and female F344/N rats and B6C3F1 mice were exposed to ground goldenseal root powder in feed for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in Salmonella typhimurium, Escherichia coli, mouse bone marrow cells, and mouse peripheral blood erythrocytes. 2-WEEK STUDY IN RATS: Groups of five male and five female rats were fed diets containing 0, 1,560, 3,121, 6,250, 12,500, 25,000, or 50,000 ppm goldenseal root powder (equivalent to average daily doses of approximately 155, 315, 630, 1,190, 2,465, and 4,815 mg goldenseal root powder/kg body weight for males and 150, 290, 640, 1,240, 2,370, and 4,870 mg/kg for females) for 15 days. All rats survived to the end of the study. Mean body weights and feed consumption of all exposed groups of males and females were similar to those of the control groups throughout the study. Liver weights of males exposed to 6,250 ppm or greater and females exposed to 12,500 ppm or greater were significantly greater than those of the controls. Minimal to moderate hepatocellular hypertrophy occurred in three males and all females exposed to 25,000 ppm and in all 50,000 ppm males and females. 2-WEEK STUDY IN MICE: Groups of five male and five female mice were fed diets containing 0, 1,560, 3,121, 6,250, 12,500, 25,000, or 50,000 ppm goldenseal root powder (equivalent to average daily doses of approximately 380, 840, 1,760, 3,435, 6,700, and 15,170 mg/kg body weight for males and 330, 670, 1,240, 2,375, 4,760, and 8,475 mg/kg for females) for 15 days. All mice survived to the end of the study. Mean body weights and feed consumption of all exposed groups of males and females were similar to those of the control groups throughout the study. Significant increases in liver weights occurred in males exposed to 25,000 and 50,000 ppm and in females exposed to 50,000 ppm. Absolute and relative thymus weights of 12,500 and 50,000 ppm males were significantly decreased. Minimal hypertrophy of centrilobular hepatocytes
occurred in all males and females exposed to 50,000 ppm. 3-MONTH STUDY IN RATS: Groups of 10 male and 10 female rats were fed diets containing 0, 3,121, 6,250, 12,500, 25,000, or 50,000 ppm goldenseal root powder (equivalent to average daily doses of approximately 255, 500, 1,000, 2,020, and 4,060 mg/kg for males and 260, 500, 1,030, 2,070, and 4,100 mg/kg for females) for 14 weeks. Additional groups of 10 male and 10 female clinical pathology study rats were given the same concentrations for 23 days. All rats survived to the end of the study. None of the body weights or mean body weight gains were significantly different from those of the controls. Feed consumption by exposed groups was generally similar to that by controls throughout the study. Liver weights were significantly increased in males exposed to 6,250 ppm or greater and in all exposed groups of females. The incidences of hepatocyte hypertrophy were significantly increased in the liver of males and females exposed to 12,500 ppm or greater; cytoplasmic vacuolization of hepatocytes occurred in all exposed males. 3-MONTH STUDY IN MICE: Groups of 10 male and 10 female mice were fed diets containing 0, 3,121, 6,250, 12,500, 25,000, or 50,000 ppm goldenseal root powder (equivalent to average daily doses of approximately 680, 1,360, 2,260, 5,370, and 10,550 mg/kg for males and 590, 1,250, 2,345, 4,790, and 10,740 mg/kg for females) for 14 weeks. All mice survived to the end of the study. Mean body weights of males exposed to 50,000 ppm and females exposed to 25,000 or 50,000 ppm were significantly less than those of the controls. Feed consumption by 3,121, 6,250, 12,500, 25,000, and 50,000 ppm males was similar to that by controls. Liver weights were significantly increased in males exposed to 12,500 ppm or greater and in females exposed to 25,000 or 50,000 ppm. The left epidydimal weight in male mice was significantly decreased relative to controls. The incidences of hepatocyte hypertrophy were significantly increased in males and females exposed to 12,500 ppm or greater. 2-YEAR STUDY IN RATS: Groups of 50 male and 50 female rats were fed diets containing 0, 3,000, 9,000, or 25,000 ppm goldenseal root powder (equivalent to average daily doses of approximately 135, 400, and 1,175 mg/kg for males and 150, 470, and 1,340 mg/kg for females) for 105 to 106 weeks. Survival of 9,000 ppm females was significantly greater than that of the controls. Mean body weights of females exposed to 9,000 ppm were 6% less than those of the controls after week 37, and those of 25,000 ppm females were 6% less than those of the controls after week 8. Feed consumption by exposed groups of males and females was generally similar to that by the controls throughout the study. The incidences of hepatocellular adenoma were significantly increased in males and females exposed to 25,000 ppm, and the incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in 25,000 ppm males. All exposed groups of males and females had significantly increased incidences of hepatocyte hypertrophy. The incidences of hepatocyte degeneration were significantly increased in all exposed groups of males and in 9,000 and 25,000 ppm females. The incidences of eosinophilic focus were significantly increased in 9,000 and 25,000 ppm males and all exposed groups of females. The incidences of cardiomyopathy were significantly decreased in all exposed groups of males and in 25,000 ppm females. 2-YEAR STUDY IN MICE: Groups of 50 male and 50 female mice were fed diets containing 0, 3,000, 9,000, or 25,000 ppm goldenseal root powder (equivalent to average daily doses of approximately 375, 1,120, and 3,275 mg/kg for males and 330, 1,000, and 2,875 mg/kg for females) for 105 to 106 weeks. Survival of 9,000 ppm females was significantly less than that of the controls. Mean body weights of females exposed to 25,000 ppm were 3% to 9% less than those of the controls after week 13, 6% less for weeks 14 to 52, and 5% less for weeks 53 to 101. Feed consumption by exposed groups of males and females was generally similar to that of
the controls throughout the study. The incidences of hepatocellular adenoma occurred with a positive trend in males, and the incidences of multiple hepatocellular adenoma were significantly increased in 9,000 and 25,000 ppm males. The incidences of hepatoblastoma occurred with a positive trend in males with a marginal increase in the 25,000 ppm group. Significantly increased incidences of eosinophilic focus or mixed cell focus occurred in all exposed groups of males. GENETIC TOXICOLOGY: Goldenseal root powder was not mutagenic in Salmonella typhimurium or Escherichia coli tester strains, with or without liver S9 metabolic activation enzymes. In addition, no increases in the frequencies of micronucleated erythrocytes were observed in peripheral blood samples from mice exposed to goldenseal root powder in feed for 3 months. Berberine chloride was also tested for mutagenicity in standard screening assays. No mutagenicity was observed in several tester strains of Salmonella typhimurium, with or without rat or hamster liver S9 metabolic activation enzymes. In an acute exposure assay, no increase in the frequency of micronucleated polychromatic erythrocytes was seen in bone marrow of male mice administered three intraperitoneal injections of berberine chloride at 24-hour intervals. CONCLUSIONS: Under the conditions of these 2-year feed studies, there was clear evidence of carcinogenic activity of goldenseal root powder in male F344/N rats based on the increased incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined). There was clear evidence of carcinogenic activity of goldenseal root powder in female F344/N rats based on the increased incidence of hepatocellular adenoma. There was some evidence of carcinogenic activity of goldenseal root powder in male B6C3F1 mice based on the increased incidences of hepatoblastoma and multiple hepatocellular adenoma. There was no evidence of carcinogenic activity of goldenseal root powder in female B6C3F1 mice exposed to 3,000, 9,000, or 25,000 ppm goldenseal root powder in feed for 2 years. Administration of goldenseal root powder resulted in increased incidences of nonneoplastic lesions in the liver of male and female rats and male mice.

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