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Two-Year Toxicity and Carcinogenicity Studies of *Panax ginseng* in Fischer 344 Rats and B6C3F1 Mice

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Abstract

Ginseng is one of the most popular herbal supplements on the US market. Numerous reports of adverse effects from products containing ginseng have been filed with the US Food and Drug Administration (FDA) and the literature documents a “ginseng abuse syndrome” among regular users. However, the chronic toxic effects of ginseng are not well characterized. Because of its significant human exposure and the fact that little information on its toxicity is available, *Panax ginseng* was nominated by the US National Institutes of Health (NIH) to the US National Toxicology Program (NTP) to assess its carcinogenic potential. In this paper, we reported the results of NTP chronic toxicity and tumorigenicity bioassay. It shows that, under these experimental conditions, *Panax ginseng* is not toxic or tumorigenic.

Keywords

Panax ginseng ; Toxicity; Carcinogenicity; Herbal Dietary Supplements

Introduction

Ginseng is a perennial aromatic herb with a short underground stem (rhizome) associated with a fleshy white root (Sticher, 1998). Ginsengs are members of the genus *Panax* in the Araliaceae family. *Panax ginseng* (Asian ginseng, also called Chinese or Korean

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ginseng) and *Panax quinquefolius* (American and Canadian ginseng) are the two most popular species in use; other ginsengs include *Panax japonicus* (Japanese ginseng), *Panax notoginseng* (Sanqui or Tienqi ginseng), *Panax elegantior* (Pearl ginseng), *Panax pseudoginseng* (Himalayan ginseng), and *Panax zingiberensis* (ginger ginseng) (Chan and Fu, 2007).

In China, *Panax ginseng* is regarded as "the all-healing man-herb." In Asia, it is considered as something of a panacea, purported to enhance stamina and endurance for both mental and physical performances, and is widely used as a geriatric tonic. It is used as an analeptic, tonic, stomach pain analgesic, and aphrodisiac (Chang et al., 1986). It has been reported that ginseng enhances cholesterol biosynthesis and serum protein synthesis and has immunomodulatory effects, anti-inflammatory activity, and antitumor activity (Foster, 1996a,b; Li et al., 2009; Jang and Shin, 2010). Evidence from *in vitro* and *in vivo* studies suggest that these actions are due to the antioxidant/nitric oxide stimulating properties (Foster, 1996a,b). In general, the effects of ginseng reported in the literature are mostly derived from observation of the use of ginseng extracts, not individual ginsenosides.

Since the Dietary Supplement Health and Education Act (DSHEA) were passed in the United States in 1994, the use of herbal products has been rapidly growing, among which ginseng has been one of the top sellers. In the United States and Western countries, ginseng has been consumed for its purported ability to enhance mental and physical stamina. Ginseng products are sold in the forms of whole root, root slices, extracts, powders, capsules, tea bags, beverages, candy, lotions, and soaps. The most popular product is Ginsana (G115 Ginseng, Pharmaton, Switzerland), a standardized product containing 4% ginseng extract, comprising more than 50% of the market.

Because ginseng products are not subject to regulatory requirements, the composition of preparations varies widely. Ginseng-induced toxicity has been reported, including adverse effects from products containing ginseng filed with the US Food and Drug Administration (FDA). In general, the reported adverse effects include CNS excitation and arousal, hypertension, nervousness, sleeplessness, skin eruptions, morning diarrhea, edema, euphoria, restlessness, agitation, insomnia, and confusion. In women, ginseng induces estrogenic effects including mastalgia with diffuse mammary modularity and vaginal bleeding in post-menopausal women (Chandler, 1988). Overexposure to ginseng has been referred to as ginseng abuse syndrome (Siegel, 1979).

Because of its significant human exposure and the fact that little information on its toxicity is available, *Panax ginseng* was nominated by the US National Institutes of Health (NIH) to the US National Toxicology Program (NTP) to assess its toxicity and carcinogenicity potential. The NTP is the US government program established to evaluate substances for health-related effects. In this paper, we report the results of the NTP study on ginseng extract including two-week repeated dose toxicity studies, three-month subchronic studies, and two-year chronic toxicity and carcinogenicity studies in rats and mice.

Materials and Methods

Materials

The ginseng extract used in the two-week repeated dose toxicity study (lot 3021261) and the three-month subchronic study (lot 302500702) was obtained from Extracts Plus, Inc. (Vista, CA, USA) and the extract used in the two-year chronic toxicity/carcinogenicity study (lot 3031978) was obtained from Plus Pharma, Inc. (Vista, CA, USA). All lots were produced by extracting *Panax ginseng* C.A. Meyer root with 80% aqueous ethanol. Identity, purity, and stability analyses were conducted based on the profile of ginsenosides in the test materials using methodologies based on the American Botanical Council's Ginseng Evaluation Program (2001). All lots of the extract were characterized as ginseng by IR spectroscopy and HPLC and comparable to authentic standards. Weight percentage of the ginsenosides in the test material was determined using the method of standard addition and analysis by HPLC. For lot 3031978 used in the two-year studies total ginsenosides were determined to be 7.4%. The infrared absorption spectrum and the weight percentages of the seven major ginsenosides, Rg1, Re, Rf, Rb1, Rc, Rb2, and Rd, of the ginseng extract were 1.5, 1.4, 0.4, 1.6, 1.0, 0.9, and 0.6, respectively (NTP, 2009). The reports of analyses are kept on file and are available for review at the National Institute of Environmental Health Sciences.

Animals

Male and female F344/N rats and B6C3F1 mice were obtained from Taconic Farms, Inc. (Germantown, NY) at four weeks of age and quarantined for 11 days before the beginning of the two-week repeated dose toxicity studies and the three-month subchronic studies. Rats and mice (from Taconic Farms at 6–7weeks of age) were quarantined for 13 (male rats), 14 (female rats), 18 (female mice), or 19 (male mice) days before the beginning of the two-year chronic toxicity/carcinogenicity studies.

Animal Treatments

In the two-week repeated dose toxicity studies, groups with five male and five female rats and mice were administered ginseng in 0.5% aqueous methylcellulose by gavage at doses of 0, 125, 250, 500, 1000, or 2000 mg/kg, five days per week for 16 days. In the three-month subchronic studies, groups of ten male and ten female rats and mice were administered ginseng in sterile water by gavage at doses of 0, 1000, 2000, 3000, 4000, or 5000 mg/kg, five days per week for 14 weeks. In the two-year chronic toxicity/carcinogenicity studies, groups of 50 male and 50 female rats and mice were administered ginseng in sterile water by gavage at doses of 0, 1250, 2500, or 5000 mg/kg, five days per week for 104 weeks. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program.

Animals were weighed individually on the first day on test, at sacrifice, and at regular intervals throughout each of the studies. The animals were observed twice daily at least six hours apart (before 10:00 AM and after 2:00 PM), including holidays and weekends, for morbidity, death, and clinical signs of pharmacologic and toxicological effects of the extract. Clinical signs were recorded daily by animal number and made a part of the study report.

Organ weights were determined for all surviving animals until the end of the study. The organs weighed were liver, thymus, right kidney, right testicle, heart, and lungs.

Necropsy and Pathology

For the two-year chronic toxicity/carcinogenicity studies, all animals received a complete necropsy examination, including those that died before the end of the study. All tissues from all animals were preserved in formalin as specified in the NTP Specifications.

Tissues were trimmed, embedded, sectioned and stained with hematoxylin and eosin for histopathologic examination.

All animals that died (or were sacrificed in a moribund condition) were subjected to a complete necropsy and slides of all tissues required for complete histopathologic evaluation were prepared and evaluated.

The tissues for complete histopathologic evaluation included adrenal glands, brain (three sections including frontal cortex and basal ganglia, parietal cortex and thalamus, and cerebellum and pons), clitoral glands, esophagus, eyes, femur, gallbladder (mouse), gross lesions, heart and aorta, large intestine, small intestine, kidneys, liver, lungs and mainstem bronchi, lymph nodes, mammary gland with adjacent skin, muscle, thigh, nasal cavity and nasal turbinates, ovaries, pancreas, parathyroid glands, pituitary gland, preputial glands, prostate, salivary glands, seminal vesicle, spinal cord and sciatic nerve, spleen, stomach (forestomach and glandular), testes with epididymis, thymus, thyroid glands, tissue masses and regional lymph nodes, trachea, urinary bladder, and uterus.

Statistical Methods

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958). Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends.

Neoplastic and non-neoplastic lesions were tested for dose-related trends and for pairwise differences from the control group using the Poly-3 test (Portier et al., 1986; Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997). The variance of the Poly-3 statistic was modified as recommended by Bieler and Williams (1993). Tests of significance included pairwise comparisons of each dosed group with the controls and a test for an overall dose-related trend. Poly-3 p-values are one sided.

Continuous variables, such as body weights, organ weights, hematology, clinical chemistry, sperm parameters, were tested for trend using Jonckheere's test (1954). If a significant trend was found (at $p < 0{:}01$), Williams' test (1971, 1972) was conducted on normally distributed endpoints and Shirley's test (1977; as modified by Williams, 1986) was conducted on non-normally distributed endpoints to determine with dose groups differed significantly from the control group. If the dose-related trend was not significant, Dunnett's test (1955) was conducted on normally distributed endpoints and Dunn's test (1964) was conducted on non-normally distributed endpoints. Prior to statistical analysis, extreme values identified

by the outlier test of Dixon and Massey (1957) were examined by NTP personnel, and implausible values were eliminated from the analysis.

Fisher exact test (Gart et al. 1979) was used to compare proportions, such as proportions of females having regular estrous cycles, between each dose group and the controls.

Results

In the two-week and three-month studies, all rats and mice were survived and there were no differences in body weights, organ weights, hematology, clinical chemistry (including serum corticosterone concentrations) that could be attributed to ginseng administration. No microscopic findings were considered attributable to ginseng administration. There were no significant differences in sperm parameters of male rats and mice or the estrous cyclicity of female rats and mice between the control and ginseng treated groups.

In the two-year chronic toxicity/carcinogenicity studies, rats and mice were administered ginseng at 0, 1250, 2500, 5000 mg/kg doses by gavage. Mean body weights of 5000 mg/kg female rats were approximately 10% lower than the controls throughout the second year of the study; otherwise, no differences were seen in body weights between the controls and treated groups of rats or mice. Survival of the 5000 mg/kg female rats at terminal sacrifice was significantly lower (48%) than the controls (72%); survival of all other dose groups of male and female rats and mice were similar to their respective controls. No treatment related increases in neoplastic lesions were observed in the treated rats and mice except the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) occurred with a positive trend in male mice (vehicle control, 12/50; 1250 mg/kg. 6/50; 2500 mg/kg, 10/50; 5000 mg/kg, 19/50; trend $p = 0.014$ by Poly-3 test); the increased incidence in the 5000 mg/kg group was not significant. Negative trends were observed in the incidences of mammary gland fibroadenomas in female rats (vehicle control, 32/50; 1250 mg/kg, 30/50; 2500 mg/kg, 30/50; 5000 mg/kg, 16/50; trend $p = 0.001$ by Poly-3 test) and ovarian cystadenomas in female mice (vehicle control, 7/50; 125 mg/kg, 2/50; 2500 mg/kg, 3/50; 5000 mg/kg, 0/50; trend $p = 0.01$ by Poly-3 test).

Incidences of the minimal to mild inflammation of the respiratory epithelium of the nose were significantly increased (pairwise $p = 0.019$ by Poly-3 test) in 5000 mg/kg female rats (vehicle control, 3/50; 1250 mg/kg, 2/50; 2500 mg/kg, 1/50; 5000 mg/kg, 10/50).

Ginseng was not mutagenic in bacterial mutagenicity assays in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA104, or TA1535. Ginseng induced no significant increases in the frequencies of micronucleated erythrocytes in the peripheral blood of male or female B6C3F1 mice exposed for three-months to 5000 mg/kg via gavage.

Discussion

The ginseng used in this study was a water/alcohol extract from the plant *Panax ginseng* C.A. Meyer in dried powder form. In the two-week toxicity studies, rats and mice were exposed to ginseng at doses up to 2000 mg/kg. There were no changes in body weights, survival, or histopathology between the dose groups and the controls both in rats and mice.

Since there were no effects at the top dose of 2000 mg/kg, the highest dose level for the 14-week subchronic studies was increased to 5000 mg/kg, the upper limit for gavage studies, for both rats and mice. In the 14-week studies, all rats and mice survived and there were no exposure-related effects on body weights, organ weights, or histopathology. Thus, in the 2-year toxicity and carcinogenicity studies in rats and mice, the dose levels were selected at 0, 1250, 2500, and 5000 mg/kg. In the two-year study, body weights of the highest dose female rats were approximately 10% less than the controls, while those of the male and female mice were similar to their respective controls. Survival of the highest dose female rats was significantly lower than the female rat controls. Survival of all other dose groups of male and female rats and mice were similar to their respective controls. The cause of early death of the highest dose female rats was not related to any histopathological and clinical changes. The deaths occurred in the last few months of the study and may not be related to treatment.

The oral LD50s of ginseng for rats and mice have been reported to be 750 mg/kg and 200 mg/kg, respectively (NLM, 1998a'b). The present study showed that rats and mice tolerated a dose as high as 5 g/kg. Thus, the oral LD50 level for rats and mice exceeded 5 g/kg. This may be due to differences in ginseng preparations or strain of test animals.

In the two-year study, the incidence of alveolar/bronchiolar adenoma or carcinoma in male mice increased with a positive trend; however, the incidence in the 5000 mg/kg group was not significantly different from the controls. The incidence (38%) was slightly above the historical range of 24–32% for gavage studies but within the range of 14–40% for all the routes. Therefore, the effects observed were not considered related to ginseng treatment. No other treatment related increases in neoplastic lesions were observed in the rats and mice. Negative trends in the incidences of mammary gland fibroadenomas in female rats and ovarian cystadenomas in female mice were observed. The decrease in incidences may be related to lower body weight.

The results of the two-year study in rats and mice are in agreement with those reported in the literature. Ginseng is considered to act in harmonizing body function according to the need of body; its activity is not specific. Epidemiologic studies have shown the reduction in risk of cancer development among people who regularly consumed ginseng and the decrease was inversely related to the dose (Yan and Choi, 1998). They concluded that *Panax ginseng* C.A. Meyer has non-organ specific preventive effects against cancer. Experimentally, red ginseng extract had anticarcinogenic effects against pulmonary, liver, mammary gland, ovarian and uterine cervix tumors induced by chemical carcinogens in mice (Yun, 2003; Yun et al., 1983, 1995; Bespalov et al., 1993, 2001; Shin et al., 2000; Panwar et al., 2005). In the present study, ginseng at a dose of 5 g/kg, the highest permissible dose level for gavage studies, did not induce neoplastic lesions. On the other hand, spontaneous tumors like mammary gland fibroadenomas in female rats and ovarian cystadenomas in female mice were decreased. The findings may be related to slightly lower body weights in the high dose female rats and mice and not necessarily considered in support of the anticarcinogenic activity of ginseng. Incidences of other spontaneous neoplasms commonly found in Fischer rats, e.g. mononuclear cell leukemia, pituitary pars distalis adenoma or carcinoma, testicular adenoma, thyroid gland C-cell adenoma, and uterine polyp, were not affected. In B6C3F1

mice, incidences of spontaneous harderian gland, liver, and lung lesions were also not affected.

Overexposure to ginseng in humans has been called ginseng abuse syndrome (Siegel, 1979). The symptoms include hypertension, gastrointestinal disturbances, insomnia, nervousness, confusion, and depression (Kitts and Hu, 2000). Cerebral arteritis has been reported to associate with consumption of a large quantity of ethanol-extracted ginseng (Ryu and Chien, 1995). In the present study, no histopathologic changes were observed in the brain tissues and no neurological or behavioral symptoms were observed in rats and mice administered ginseng at a dose as high as 5000 mg/kg.

It has been postulated that the diverse effects of ginseng may be related to its modulation of hormones. The present study found no evidence of hormonal effects in rats or mice.

It is worthwhile to compare the findings of this study with the Chinese medicinal reports. “Shen Nong’s Herbal Classic” (神農本草經) is a more than 2000-year old Chinese medicinal book and the oldest book on herbal medicine in China (Shen, 1998). This book classified 365 herbal species, animals, and minerals into three categories: the First Category (Superior Class), the Second Category, and the Third Category. Based on this book’s compilation, the medicines belonging to First Category are effective for multiple diseases, mostly responsible for maintaining and restoring the body balance, and almost no unfavorable side effects. Consequently the medicines in this category can be taken daily for a long period of time without causing side effects. *Panax ginseng* was ranked among the top medicines in the First Category, and was therefore the most exalted medicine in ancient times. Therefore, the findings that *Panax ginseng* does not exert toxic or carcinogenic effects in the NTP two-year study in F344 rats and B6C3F1 mice are consistent with this Chinese herbal medicinal report. However, since adverse health effects of ginseng have been reported, further investigation into the cause of these effects is warranted.

Currently, because of popular use of herbal products worldwide, the safe use of herbal products is a serious concern. Since the United States Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994, sales and presumably use of herbal products have been rapidly growing in the United States. The American Herbal Products Association estimates that in 2004 there were about 3000 species of plants, in as many as 50,000 different products, sold as herbal supplements in the United States (Zurer and Hanson, 2004). To date, safety issues concerning potential side effects and toxic contamination of herbal products have not been addressed adequately. The identification and risk assessment of the toxic ingredients, including genotoxic and tumorigenic ingredients in many raw herbs have not been systematically studied (Hu et al., 2005; Singh, 2005; Chan et al., 2007; Fu et al., 2008, 2009; Guo et al., 2008, 2009, 2010a,b). Consequently, the quality and safety of herbal dietary supplements, as well as the raw herbal plants used for dietary supplement preparations, must be assured (CDC, 2002; CFSAN, 2001a and 2001b, 2002; CFSAN, 2004; Lin et al., 2010). To date, more than 30 herbal dietary supplements and active ingredients have been nominated by the US FDA and the NIH for testing by the US NTP for determination of their toxicity and tumorigenicity. The herbal dietary supplements that have been tested or are being tested include *Aloe vera, Panax ginseng,* kava, *Ginkgo*

biloba extract, green tea extract, comfrey, symphytine, dong quai, ephedrine alkaloid, L-ephedrine (ma huang), black cohosh, goldenseal root powder, pulegone, usnic acid, Usnea herb, and berberine. The NTP chronic carcinogenicity bioassay results are highly useful references for supporting regulatory decisions made by the US federal agencies.

In conclusion, there was no evidence of toxicity and carcinogenic activity of ginseng in male or female F344/N rats or B6C3F1 mice administered ginseng at up to 5000 mg/kg. Furthermore, *Panax ginseng* is not genotoxic.

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