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PIYARAT JITRAWANG: EFFECT OF STEVIOSIDE AND STEVIOL ON REPRODUCTIVE CAPABILITY AND MICRONUCLEUS FORMATION IN HAMSTERS. THESIS ADVISORS : PUNYA TEMCHAROEN, D.V.M., M.Sc., CHAIVAT TOSKULKAO, D.V.M., Ph.D., THIRAYUDH GLINSUKON, Sc.D.
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Stevioside is a sweet glycoside derived from the leaves of *Stevia rebaudiana*. It is widely used as a non-caloric sugar substitute because of its sweetener property; approximately 300 times sweeter than sucrose. Stevioside has been evaluated in various studies for safety and most of these studies showed no serious toxic effects. Steviol, diterpenic carboxylic alcohol, is a major metabolite of stevioside. It showed dose-related positive responses in a forward mutation assay using *Salmonella typhimurium* TM677, chromosomal aberration test and a gene mutation assay using Chinese hamster lung fibroblast cell line. The possibility exists that substances administered to males before mating may induce changes transmissible to their pups. Therefore, we conducted the experiments to evaluate the effects of stevioside and steviol on reproductive capability after administration to males. Additionally, *in vivo* micronucleus tests were also performed to evaluate the genotoxic effects of these compounds. Male hamsters were given stevioside at the doses of 0, 500, 1000, 2500 mg/kg BW/day and steviol at the doses of 0, 100, 250, 400 mg/kg BW/day by oral intubation on 5 consecutive days, for 8 weeks. There were no deaths or clinical signs of toxicity in male hamsters given the various doses of stevioside, through with steviol at a dose of 400 mg/kg BW/day, a decrease in body weight was observed. A reduction of growth rate was also observed in male hamsters treated with a high dose of steviol (500 mg/kg BW/day). Furthermore, seven hamsters died during the treatment period and two died during the mating period. Plasma biochemical examination showed an elevation of BUN and creatinine, markers of renal damage, in hamsters given the high doses of stevioside (2500 mg/kg BW/day) and steviol (400 and 500 mg/kg BW/day). In the reproductive study, each male was mated with 2 untreated females (1Male: 1Female for each week) after treatment period for 2 weeks. Thereafter, pregnant females were kept to term and allowed to deliver normally. During lactation period, pup parameters were observed including pup body weight, body weight gain, litter size, organ weight, gross anomalies and histopathological changes. Neither stevioside nor steviol caused any adverse effects on fertility or general reproductive parameters in dams and pups. The mutagenic activity of stevioside and steviol were also investigated by using the bone marrow micronucleus test. After 8 weeks of stevioside and steviol treatment, bone marrow samples were obtained and scored for micronucleated polychromatic erythrocytes (MNPCEs) in bone marrow content. Neither stevioside nor steviol at any dose used yielded any significant increase in the frequencies of MNPCEs at any post-treatment sampling times (24, 48 and 72 h).