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Increasing evidence regarding free radical generating agents and inflammatory processes suggests that accumulation of reactive oxygen species can cause hepatotoxicity. A short-chain analog of lipid hydroperoxide, t-butyl hydroperoxide (t-BHP), can be metabolized to free radical intermediates by cytochrome P-450 in hepatocytes, which in turn can initiate lipid peroxidation, affect cell integrity and result in cell injury. In this study, we used t-BHP to induce hepatotoxicity and determined the antioxidative bioactivity of aqueous extract from the roots of Platycodon grandiflorum A. DC (Campanulaceae), Changkil (CK). Pretreatment with CK prior to the administration of t-BHP significantly prevented the increase in serum alanine aminotransferase and aspartate aminotransferase activity and hepatic lipid peroxidation in a dose-dependent manner. Hepatic glutathione level was not affected by treatment with CK alone, but pretreatment with CK protected the t-BHP-induced depletion of hepatic glutathione levels. Histopathological evaluation of the rat livers revealed that CK reduced the incidence of liver lesions induced by t-BHP, including hepatocyte swelling, leukocyte infiltration, and necrosis. Based on the results described above, we speculate that CK may play a hepatoprotective effects via reducing oxidative stress in living systems.

[PA4-12] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

The flavonoid quercetin inhibits dimethylnitrosamine-induced hepatic fibrosis in rats

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Quercetin, one of the most abundant flavonoids in human diet has been reported to exhibit a wide range of pharmacological properties. In this study, we investigated the protective effect of quercetin on hepatic fibrosis induced by dimethylnitrosamine (DMN) in rats. Treatment with DMN caused a significant decrease in body and liver weight. Oral administration of quercetin (10 mg/kg daily for 4 weeks) remarkably prevented this DMN-induced loss in body and liver weight and inhibited the elevation of serum alanine transaminase, aspartate transaminase, and bilirubin levels. Quercetin also increased serum albumin and hepatic glutathione levels and reduced the hepatic level of malondialdehyde. Furthermore, DMN-induced elevation of hydroxyproline content was reduced in the quercetin treated animals, the result of which was consistent with histological analysis of liver tissue stained with Sirius red. A reduction in hepatic stellate cell activation, as assessed by 깱-smooth muscle actin staining, was associated with quercetin treatment as well as a reduction in transforming growth factor-깱1 expression. In conclusion, these results demonstrate that quercetin exhibited in vivo hepatoprotective and anti-fibrogenic effects against DMN-induced liver injuries and suggest that quercetin may be useful in the prevention of hepatic fibrosis development.

[PA4-13] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Toxicological Evaluation of Oriental Herbal Medicine Kamijadowhan Preparations

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Choi group reported that Kamijadowhan (KMD), an oriental herbal medicine, has anti-angiogenic effects and it may be a potential agent for clinical chemoprevention since it inhibits angiogenesis. Objectives of this experiment are to investigate acute, genetic and reproductive/developmental toxicities of KMD preparations. Acute toxicity was performed after single administration of KMD (200~500 mg/kg) to mice. Supravital staining micronucleus assay was conducted using peripheral reticulocytes in mice. Thymidine kinase (tk+/-) gene forward mutation was tested in mouse lymphoma L5178Y cell line, and *Salmonella*/histidine reversion assay was tested using TA 98 and TA 100. Reproductive/developmental toxicity was performed in pregnant rats treated with two different dose of KMD. MTT-based cytotoxicity in Neuro-2A cell line was measured. In acute toxicity test using mice given KMD intraperitoneally (200~5000 mg/kg), LD_{50} value was decided to be >5000 mg/kg. The tk+/- forward gene

mutation and *in vivo* supravital staining assays showed no significant increases of mutation frequency and micronucleated reticulocytes in the presence and absence of S-9 metabolic activation system at various concentrations of KMD (313, 625, 1250 and 2500 ㎍/㎖), respectively. In reproductive/developmental toxicity test, no significant alterations in developmental physical landmarks in offspring, maternal weight gain during gestation and post-gestation, and offspring weight were observed in KMD-treated groups. In *Salmonella*/histidine reversion assay, two different kinds of KMD preparations (KMD and NKMD) were showed no significant increases of His+ revertents and dose-dependency. Cytotoxicity of KMD and NKMD preparations was observed in neuro-2A cells at concentrations of more than 100 ㎍/㎖, where morphological changes were observed.

[PA4-14] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

The Effect of Chondroitin Sulfate against Oxidative Stress and Atherosclerosis in Ovariectomized Rat

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The surgically ovariectomized rat induces aging by reactive oxygen species(ROS) generation. Free oxygen radicals have been proposed as important causative agents of aging. The purpose of this study was to investigate the effect of Chondroitin Sulfate(CS) to prevent ovariectomy(OVX) induced oxidative stress and atherosclerosis. The OVX rats were given intraperitoneally CS at dose of 100mg/kg and 200mg/kg daily for fifteen weeks. Malondialdehyde(MDA) levels were determined as well as the activities of superoxide dismutase(SOD), catalase(CAT), reduced-glutathione(GSH), oxidized-glutathione(GSSG), glutathione peroxidase(GPx) in the liver (total homogenate and mitochondrial fraction). Histopathology of liver tissue was also investigated. Liver antioxidative enzyme activity was elevated while MDA concentration decreased in all CS treated animals. The results demonstrated that CS protected oxidative stress in a dose dependent manner. Moreover, inflammation and cirrhosis in liver tissue of CS treated group were significantly decreased. In addition, level of total cholesterol(TC), HDL-cholesterol, LDL-cholesterol, total lipid(TL), and triglyceride(TG) in ovariectomised rat blood were examined. And then, atherosclerotic index(AI) was calculated. Based on the results, intraperitoneally inoculated CS against peroxidation was retarded the progression of atherosclerosis. These results suggest that CS might be a useful candidate for antioxidative reagent.

[PA4-15] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Hepatoprotective effects of Platycodi Radix on carbon tetrachloride-induced liver damage in mice

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The protective effects of a Platycodi Radix (Changkil: CK), the root of Platycodon grandiflorum A. DC (Campanulaceae), on carbon tetrachloride-induced hepatotoxicity and the possible mechanisms involved in this protection were investigated in mice. Pretreatment with CK prior to the administration of carbon tetrachloride significantly prevented the increased serum enzymatic activities of alanine and aspartate aminotransferase in a dose-dependent manner. In addition, pretreatment with CK also significantly prevented the elevation of hepatic malondialdehyde formation and the depletion of reduced glutathione content in the liver of carbon tetrachloride-intoxicated mice. However, hepatic reduced glutathione levels and glutathione-S-transferase activities were not affected by treatment with CK alone. Carbon tetrachloride?induced hepatotoxicity was also essentially prevented, as indicated by a liver histopathologic study. The effects of CK on the cytochrome P450 (P450) 2E1, the major isozyme involved in carbon tetrachloride bioactivation were also investigated. Treatment of mice with CK resulted in a significant decrease of P450 2E1-dependent p-nitrophenol and aniline hydroxylation in a dose-dependent manner. CK showed antioxidant effects in FeCl2-ascorbate induced lipid peroxidation in mice liver homogenate and in superoxide radical scavenging activity. Our results suggest that the protective effects of CK against carbon tetrachloride-induced hepatotoxicity possibly involve mechanisms related to its ability to block P450?mediated carbon tetrachloride bioactivation and free radical scavenging effects.