STUDIES ON THE HEPATOPROTECTIVE EFFECTS OF RUTIN

A.H. Gilani, K.H. Janbaz and S.A. Saeed, Department of Pharmacology, The Aga Khan University Medical College, Karachi-74800, Pakistan.

Rutin is a well known flavonoid found in *Artemesia scoparia* and some other plants. It exhibits multiple actions such as spasmolytic and inhibition of arachidonic acid metabolism. In this study we describe a new activity (hepatoprotective) in an animal model of hepatotoxicity.

Wistar rats were divided into 3 groups of 10 each. Group 1 served as control and received saline (10 mL/kg) and vehicle (1% methylcellulose; 13 mL/kg) orally. Group 2 was given 4 doses of saline at 12 hrs interval and paracetamol was administered orally 1 hr post-treatment of the last dose. Group 3 was treated similar to that of group 2, except that rutin (20 mg/Kg) was administered instead of saline. In a parallel study on 3 similar groups, the treatment remained same except that paracetamol was replaced by CCl_4 and vehicle was changed to olive oil (7.5 mL/Kg). Liver function was assessed after 24 hr of toxin administration by measuring serum GOT and GPT.

Paracetamol (640 mg/kg) produced liver damage as manifested by the rise in serum levels of GOT and GPT to 1013 ± 258 and 686 ± 219 1U/L (n=10) compared to respective control values of 118 ± 6 and 39 ± 07. Pretreatment of animals with rutin lowered ($P<0.01$) the respective serum GOT and GPT levels to 145 ± 22 and 61 ± 15. Similarly, CCl_4 (1.5 mL/Kg) raised ($P>0,01$) the serum GOT and GPT levels to 853 ± 252 and 551 ± 196 1U/L (n=10) compared to respective control values 111 ± 13 and 40 ± 10. Rutin was also able to prevent ($P<0.05$) the CCl_4-induced rise in serum enzymes and the estimated values of GOT and GPT were 153 ± 27 and 64 ± 24 respectively.

These data indicate that the rutin exhibits hepatoprotective action against both paracetamol and CCl_4-induced liver damage and the presence of rutin as a plant constituent in the *Artemesia scoparia* may be responsible for the folkloric use of the plant in liver damage.

EFFECTIVENESS OF PHYTIN FOR RESTORATION OF LIVER FUNCTIONAL STATE IN ACUTE LESION.

H.Y.Karimov, F.H.Inoytova, Z.Z.Hakimov.
Second Medical Institute, 2 Farobi street, 700109 Tashkent, Republic of Uzbekistan.

Acute hepatic lesion by thioacetamide (200mg/kg) is distiguished by disorders of microcirculation, transcapillary exchange, hypoxy and consequently by intensification of biomembranes lipid peroxidization and inhibition organells membranolinked enzyme system activity. An experimental treatment with phytin(200mg/kg)within 3 days and in particular 6 days period led up to restoration the microcirculation channel and hepatic blood stream velocity. 3 daily administration phytin decreased content of acylhydroperoxidases 2,29 and 1,31, malon dialdehyde 2,1 and 1,66 times, as well as increased catalase activity in microsomal and mitochondrial fractions. Prolongation of phytin administration intensified its antioxidant features. All this stipulated increasing the level of cytochrome P-450 3,67 and 8,0 times and anilinhydroxilase 1,42 and 2,84 times in microsomal fraction in accordance with terms and reached control evaluations. It was noted and high-energy change for the better and increase the conjugation and effectiveness of oxiding phosphorylation in mitochondria. Antioxidant, membranostabilizing and soft inductive action of phytin on intracellular processes allowed to recommend its application in hepatology.

Inhibitory Effects of H_2-Receptor Antagonists on Cytochrome P450 *In Vitro* and *In vivo*

Eun-Joo Kim, Sang Seop Han, Jung Koo Roh, Tae Cheon Jeong
Toxicology Research Center, Korea Research Institute of Chemical Technology
P.O. Box 107, Yusung-Ku Taejon, Korea

The present study was undertaken to examine the effects of H_2-receptor antagonists including newly developed mifentidine derivatives, IY-80843 and IY-80845, N-[2-(4-Methoxyphenyl) ethyl]-N'-[4-(Imidazole-4-yl)phenyl] formamidine, on cytochrome P450(P450) *in vitro* and *in vivo*.

Initially, 3-methylcholanthrene-, phenobarbital-, ethanol- and dexamethasone-induced liver microsomes were prepared from male ICR mice to study in vitro effects of above chemicals on ethoxyresorufin *O*-deethylase(EROD), pentoxyresorufin *O*-dealkylase(PROD), *p*-nitrophenol hydroxylase and erythromycin *N*-demethylase(ERDM) activities, respectively. It was found that histamine, cimetidine and famotidine were not inhibitory to four enzyme activities. Meanwhile, mifentidine slightly inhibited EROD and PROD activities and its derivatives IY-80843 and IY-80845 strongly inhibited PROD, EROD and ERDM activities.

Prolongation of hexobarbital-induced sleeping time was determined in male ICR mice to confirm *in vitro* inhibitory effects of mifentidine and its derivatives *in vivo*. It was observed that cimetidine, mifentidine, IY-80843 and IY-80845 caused dose-dependent increase in the sleeping time, indicating the inhibition of P450 for hexobarbital metabolism.

It was concluded that mifentidine and its derivatives are P450 inhibitors and that our newly synthesized IY-80843 is most inhibitory.

The present results indicate that mifentidine and its derivatives not only antogonize the H_2-receptor but also inhibit P450 enzymes.

SYMPHYTUM OFFICINALE (L) GAERTN - A PROSPECTIVE HEPATOPROTECTIVE AND HEPATOREGENERATIVE PLANT

C. Matcovschi, Z. Calistru, M. Cojocaru, S. Vâlcu
Pharmaceutical Center, 2 Corolenco str., Chisinau, Moldova.
International University of Moldova, 198 Stefan cel Mare Avenue, Chisinau, Moldova.

The medication of Chronic Liver Disease and hepatocirrhosis are among the major problems of our country, where these diseases are very spread. From European medicine experience it is known that the medication of Chronic Liver Diseases is more efficient using vegetable drugs and the most efficient among them is Silibum marianum L. The popular medicine of Moldova uses successfully Symphitum officinale ("black root" or in Italian "radice nera") for saving the patients with persistent chronic hepatitis and hepatocirrhosis. Our experiments were made on 42 white rats (wt. 180-240g)": 28 with chronic toxic hepatitis induced by tetraclormetan(20ml/kg twice a week during 2 months) and 14 intact animals. The sick rats were divided into 3 groups: 1)not treated, 2)treated with Silibor 30mg/kg daily during 2 weeks 3)treated with dense alcoholic extract of Symphytum officinale 0,4g/kg per os daily during 2 weeks. We've studied the values of ALT, proteic toxins with average weight and lipids concentration in liver tissue. The obtained results shows that the dense extract of Symphytum officinale produces effects statistically significant, equal or superior to Silibor. The hepatoprotective effects are: the decreasing of lipidodistrophy and the absence of conjunctive prolipheration in the interlobular grooves. We intend to find out the active compound of this plant.