J. Korean Soc. Food Nutr.
21(3), 291 ~ 295 (1992)

The Pharmaco-chemical Study on the Plant of *Ixeris* spp.
1. Anti-hypercholesterolemic Effect of *Ixeris sonchifolia*

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Abstract

The methanol extracts from different parts of *Ixeris sonchifolia* (Compositae) were evaluated for their total cholesterol lowering effect in mice. Mice were rendered hypercholesterolemic with 1% cholesterol and 0.5% cholic acid. Significant lowering in serum cholesterol was observed in mice with the methanol extract from leaves (MeOH-LF), whereas the methanol extract from roots (MeOH-RT) was devoid of this effect. In rats with cholesterol-induced hyperlipidemia MeOH-LF in a dose of 100mg/kg body weight caused significant decrease of total cholesterol, and the atherogenic index was also improved. On the other hand, total cholesterol in rats fed a stock diet was not affected by administration of the MeOH-LF. Thus, it is suggested that this MeOH-LF probably may increase the metabolic utilization only when fed with excess cholesterol.

Key words : *Ixeris sonchifolia* (Compositae), total cholesterol, atherogenic index

INTRODUCTION

Species of the genus *Ixeris* (Compositae) are used in strengthening the stomach, as sedatives and as diuretic agents[1]. Among them, the whole plants of *Ixeris sonchifolia* have been used as a traditional Kimchi in Korea. It was previously reported that the whole plants contain sugars, amino acids, fatty acids and polyphenols[2]. However, no extensive chemical and pharmacological studies about this plant have been done yet.

In the course of screening for hypocholesterolemic drugs among Korean folk medicines, we found that intraperitoneal administration of methanol extract of *I. dentata* resulted in a significant decrease of blood total cholesterol in hypercholesterolemic mice[3].

The present study was undertaken to provide the possibility as an anti-cholesterolemic drug of *I. sonchifolia* in hypercholesterolemic rats. This paper also reports the effect of the methanol extracts from different parts (leaves and roots) on serum cholesterol in hypercholesterolemic mice, and the effect of the methanol extract from leaves (MeOH-LF) on normal rats.

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MATERIALS AND METHODS

Animals

Male rats (150~160g) of the Spague-Dawley strain and male mice (20~22g) of the albino dd strain were maintained in an air-conditioned room with lighting from 06 : 00 to 18 : 00h. The room temperature (about 25° C) and humidity (about 60%) were controlled automatically. A laboratory pellet chow (obtained from Purina Feed Ltd., Korea) and water were given freely.

Hypercholesterolemic mice

A group of mice weighing 22±2g were placed on a diet consisting of Purina pellets supplemented with 1% cholesterol and 0.5% cholic acid. Seven days after intake of the experimental diet, blood was drawn from the orbital sinus with micro-hematocrit tubes, and mice with a total cholesterol level of 100 mg/dl or more were used as hypercholesterolemic mice.

Hypercholesterolemic rat

A group of rats weighing 170±10g were placed on a diet consisting of Purina pellet supplemented with 1% cholesterol and 0.5% cholic acid. Seven days after intake of the experimental diet, blood was drawn from the tail vein with micro-hematocrit tubes, and rats with a total cholesterol level of 200mg/dl or more used as hypercholesterolemic rats.

Preparation of methanol extract

Dried roots and leaves (each, 1kg) of commercially available *I. sonchifolia* were extracted with methanol under reflux. The extracts were concentrated to dryness *in vacuo* at 40° C to produce the methanol extract (yield : 165g from roots and 135g from leaves).

Experimental procedure

The methanol extracts suspended in 5% ethanol-saline were each administered intraperitoneally once a day for 3 days to animals at the indicated dose, while control animals were treated with an equal volume of 5% ethanol-saline. Rats were sacrificed at 2 p.m., 4 hours after the last dose. Blood was collected and allowed to stand for several hours in a cold room at 4° C. Serum was separated by contrifugation (1,000 x g, 10 min).

Determination of total cholesterol, low-density lipoprotein (LDL) - cholesterol, and high-density lipoprotein (HDL) - cholesterol in serum

Total cholesterol was determined using commercial reagent (Cholestezyme-V, Eiken Chem. Co., Japan). LDL- and HDL-cholesterol was determined by the method of Noma *et al*[4,5].

Statistics

The significance of difference between the control and methanol extract-treated groups was tested using Student's t-test.

RESULTS AND DISCUSSION

Hypercholesterolemia is one of the risk factors for atherosclerosis in general and coronary heart disease in particular[6,7], and can be divided broadly into two categories : First, an exogenous hypercholesterolemia and second, an endogenous hypercholesterolemia. These are brought about by an excessive intake of cholesterol and an excessive production of cholesterol in the liver, or a lowering catabolism of cholesterol, respectively.

Hypercholesterolemia in atherosclerotic patients, however, can't be adequately controlled by dietary regulation alone. Thus, many well-tolerated hypocholesterolemic drugs, includings plant origin, are widely used for the improvement of hypercholesterolemia associated atherosclerosis[8,9].

A high-cholesterol diet has been known to cause hyperlipidemia, and there is a close relationship between atherosclerosis with an increase of serum lipids. In particular, very-low-density lipoprotein (VLDL) and LDL may be risk factors, and HDL may be a preventive factor[10].

In the present study, we investigated effects of the extracts of *I. sonchifolia* on lipid levels after repeated intraperitoneal administration in an animal experimental model with hypercholesterolemia.

Animals fed with the experimental diet showed almost double the total cholesterol level as those fed with a stock diet (Table 1 and 2 *vs* 3).

Table 1 shows the effect on the level of total cholesterol after repeated intraperitoneal administration of the methanol extracts from different parts (leaves and roots) of *I. sonchifolia* at a dose of 100

mg/kg or 200mg/kg in hypercholesterolemic mice.

Significant lowering effect (about 25%) in serum cholesterol was observed in mice with the methanol extract from leaves (MeOH-LF), whereas the methanol extract from roots (MeOH-RT) was devoid of this effect. The lack of hypocholesterolemic effect of MeOH-RT may be considered partly due to the difference of chemical composition.

Table 1. Effect of the methanol extracts from different parts (leaves and roots) on total cholesterol of hypercholesterolemic mice

Treatment	Dose (mg/kg body wt)	Total cholesterol (mg/dl)
Control	-	140.40± 6.18 (100)
MeOH ext.	100	146.39±11.75 (104)
(root)	200	129.40± 5.00 (92)
Control	-	162.68± 8.53 (100)
MeOH ext.	100	123.34± 7.37 (76)**
(leaves)	200	120.70±12.86 (74)**

Values are mean±S.E.
Figures in parentheses are percentages of the control value
Significantly different from the control value : **$p<0.01$

Table 2 shows the effects on serum constituents after intraperitoneal administration of the MeOH-LF at 100 and 200mg/kg. Rats in the MeOH-LF-treated group showed a significant decrease of total cholesterol in dose dependent manners. Total cholesterol was significantly lowered by as much as 34 and 46% in the groups given doses of 100 and 200 mg, respectively. Table 2 also shows the changes in serum lipoprotein concentrations and the atherogenic index (AI=total cholesterol−HDL- cholesterol /HDL-cholesetrol). Rats in the 100-mg dose group showed a decrease of LDL-cholesterol with a concomitant slight increase in the level of HDL-cholesterol. The atherogenic index was also significantly reduced in the MeOH-LF-treated groups as compared with the control group. Because apo-B-containing lipoprotein fractions are thought to be responsible for cholesterol deposition in atherosclerotic plaques[11], a reduction in LDL would be advanatgeous clinically, and in fact it was shown clearly that the MeOH-LF had an improving effect on the hyperlipidemia induced by a high-choles-

Table 2. Effect of the methanol extract of *I. sonchifolia* (leaves) on serum levels in rats fed on a high cholesterol diet

Treatment	Dose (mg / kg)	TC[a] (mg / dl)	HDL-C (mg / dl)	LDL-C (mg / dl)	A.I.
Control	-	242.77±27.46 (100)	10.89±1.19 (100)	101.29±11.41 (100)	21.89±2.58 (100)
MeOH ext.	100	159.85±15.41 (66)*	13.95±2.25 (128)*	59.30±8.27 (59)**	11.87±2.26 (54)**
MeOH ext.	200	129.87±15.62 (54)**	10.32±1.33 (95)	50.39±7.68 (50)**	13.09±3.20 (60)*

Values are mean±S.E. for six to seven rats. Figures in parentheses are percentages of the control value
[a]TC = total cholesterol ; HDL-C = high density lipoprotein-cholesterol ; LDL-C = low density lipoprotein-cholesterol ; A.I. = atherogenic index
*Significantly different from the control value, $p<0.05$, **$p<0.01$

Table 3. Effect of the methanol extract of *I. sonchifolia* (leaves) on serum levels in normal rats

Treatment	Dose (mg / kg)	TC[a] (mg / dl)	HDL-C (mg / dl)	LDL-C (mg / dl)	A.I.
Control	-	54.71±1.66 (100)	21.05±2.63 (100)	11.02±6.92 (100)	1.78±0.78 (100)
MeOH ext.	100	54.92±2.61 (100)	21.40±0.93 (102)	10.92±3.84 (99)	1.66±0.42 (93)
MeOH ext.	200	49.80±2.54 (91)	17.89±2.86 (85)	12.52±3.12 (114)	2.45±0.46 (138)

Values are mean±S.E. for six to seven rats. Figures in parentheses are percentages of the control value
[a]TC = total cholesterol ; HDL-C = high density lipoprotein-cholesterol ; LDL-C = low density lipoprotein-cholesterol ; A.I. = atherogenic index

terol diet.

This is thought to be the first report on the hypocholesterolemic effect of an extract from *Ixeris* species in rats with hyperlipidemia due to high-cholesterol feeding.

Compared with the significant decrease in serum cholesterol in rats with high-cholesterol fed hyperlipidemia, the levels of such parameters in rats fed with a stock diet were not affected (Table 3).

From the results obtained, we demonstrated that the MeOH-LF did not exert hypolipidemic effect in normal rats and we additionally point out that this MeOH-LF may probably increase the metabolic utilization only when fed with excess cholesterol.

The findings of the present work indicate that the methanol extract of *Ixeris sonchifolia* leaves may be useful for treatment of hyperlipidemic disease. Further comprehensive chemical and pharmacological investigations to elucidate the exact mechanism of these effects and to isolate the active principles responsible are now in progress.

ACKNOWLEDGEMENT

The study was supported by a grant from Korea Research Foundation, 1990.

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(Received May 28, 1992)

Ixeris 속 식물의 약화학적 연구
1. 고들빼기의 고콜레스테롤혈증 개선효과

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요 약

고들빼기의 부위별 메탄올 엑스가 고콜레스테롤 생쥐의 혈청 콜레스테롤농도에 미치는 영향을 살펴보았다. 고콜레스테롤 생쥐는 식이에 1% 콜레스테롤과 0.5%담즙산을 첨가하므로서 유도하였으며, 잎의 메탄올 엑스를 투여한 군은 대조군에 비해 혈청 콜레스테롤 농도를 현저히 감소시켰으나 뿌리의 경우에는 효과가 나타나지 않았다. 또한, 잎의 메탄올 엑스는 고콜레스테롤 흰쥐에 대해서도 100mg/kg 투여 용량에서 혈청 콜레스테롤 농도를 현저히 감소 시켰으며 동맥경화성 지표를 개선시켰다. 반면에, 정상흰쥐에 대해서는 효과가 나타나지 않았다. 이상과 같은 결과로 잎의 메탄올 엑스는 과잉의 콜레스테롤을 섭취하였을때 체내대사 이용도를 증가시키므로서 혈청 콜레스테롤 농도를 감소시킨다고 생각된다.