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Anti-lipid Peroxidative Principles from the Stem Bark of *Kalopanax pictus* Nakai

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Hepatic lipid peroxide contents were examined in bromobenzene-treated rats firstly after the oral administration of MeOH extract of *Kalopanax pictus* stem bark, its n-BuOH fraction, EtOAc fraction and an alkaline hydrolysate of the n-BuOH fraction, and secondly after the intraperitoneal administration of hederagenin monodesmosides and bisdesmosides. Two hederagenin monodesmosides, kalopanaxsaponin A (KPS-A) and sapindoside C, exhibited significant anti-lipid peroxidation effects after intraperitoneal administration at doses of 10-30 μmole/kg, whereas their bisdesmosides did not exhibit any significant activity. These results suggest that it is the hederagenin monodesmosides that are responsible for anti-lipid peroxidation *in vivo*. The activity of KPS-A was established by the observation of decreased aminopyrine N-demethylase activity and increased epoxide hydrolase activity.

Key words: *Kalopanax pictus*, Araliaceae, Lipid peroxidation, Malondialdehyde, Saponin

INTRODUCTION

Kalopanacis Cortex, a folkloric medicine originating from the stem bark of *Kalopanax pictus* Nakai (Araliaceae), has been used in Korea as a therapeutic for treatment of adult diseases such as rheumatoidal arthritis, neurotic pain and diabetes mellitus (Kim, 1996). The constituents of the crude drug involve series of hederagenin glycosides and some phenolics (Sano *et al.*, 1991; Shao *et al.*, 1989a and 1989b). We have previously reported that kalopanaxsaponin A (KPS-A) was a potent anti-diabetic agent (Park *et al.*, 1998), and that major saponins, kalopanaxsaponin B and H could be converted to each corresponding monodesmoside, kalopanaxsaponin A and I, by human intestinal bacteria (Kim *et al.*, 1998). We have also reported that the essential moieties of hederagenin glycosides were responsible for antimutagenic and cytotoxic activity (Lee *et al.*, 2000). Many researchers (Saito *et al.*, 1993; Park *et al.*, 1999; Quetin-Leclercq *et al.*, 1992) have reported that the biological activities of the triterpene monodesmosides were quite different from those of their bisdesmosides. Some hederagenin monodesmosides such as a-hederin and sapindoside B protected hepatotoxicity in mice (Jeong *et al.*, 1998; Shi *et al.*, 1996), while all the hederagenin bisdesmosides exhibited cytoprotective action against the hepatocyte (Saito *et al.*, 1993). Against expectations, we have found the antimutagenic activity of hederagenin monodesmosides and bisdesmosides may be due to the suppression of cytochrome P_{450} enzymes (Park *et al.*, 2000).

In the present study, the anti-lipid peroxidation activities of hederagenin glycosides isolated from the stem bark of *Kalopanax pictus* were evaluated in bromobenzene-treated rats. Hepatic drug-metabolizing enzyme activities were also investigated in KPS-A pretreated rats.

MATERIALS AND METHODS

Plant material

Kalopanax pictus Nakai was collected in August, 1998 in Kangwon province, Korea, and the plant was identified by Prof. S.Y. Yun (Division of Applied Plant Sciences,

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Sangji University, Wonju, Korea). A voucher specimen (# NATCHEM-19) was deposited in the herbarium of Life Science and Natural Resources, Sangji University, Wonju, Korea.

Extraction, fractionation and isolation

Dried stem bark (4.8 kg) of *Kalopanax pictus* was cut and extracted three times under reflux. The extract was filtered and evaporated on a rotary evaporator under reduced pressure to give a viscous mass (630 g) of MeOH extract, which was fractionated and isolated as reported previously (Park *et al.*, 1998). A saponin (**3**), different from compounds **1** and **2** that have been isolated previously by ourselves (Park *et al.*, 1998), was obtained in the pure state (1.2 g). Saponin **3** was identified as 3-O-β-D-glucopyranosyl (1 →4)-β-D-xylopyranosyl (1 →3)-α-L-rhamnopyranosyl (1 →2)-α-L-arabinopyranosyl-23-hydroxyolean-12-en-28-O-α-L-rhamnopyranosyl (1-4)-β-D-glucopyranosyl (1-6)-β-D-glucopyranosyl ester by comparisons of physicochemical and spectral data with the literature data which have been isolated from this plant (Lee *et al.*, 1991). For convenience we designated **3** as kalopanaxsaponin K.

1 *(Kalopanaxsaponin B, 1.9 g)*: Amorphous powder, mp 204-212°C (dec.), ^{1}H-NMR and ^{13}C-NMR: literature (Kim *et al.*, 1998).

2 *(Kalopanaxsaponin H, 1.3 g)*: Amorphous powder, mp 212-217°C (dec.), ^{1}H-NMR and ^{13}C-NMR: literature (Kim *et al.*, 1998).

3 *Kalopanaxsaponin K, 1.2 g)*: Amorphous powder, mp 217-219°C (dec.), ^{1}H-NMR and ^{13}C-NMR: literature (Lee M *et al.*, 1991).

Preparation of kalopanaxsaponin A (5), I (6), and K (7)

To obtain hederagenin monodesmosides from the stem bark of *Kalopanax pictus*, n-BuOH fraction (15 g) from the MeOH extract of the plant was partially hydrolyzed in 2%-NaOH {MeOH-H_2O (2:8, v/v), 300 ml} solution for 40 min under reflux. After cooling, the reaction mixture was acidified with d-HCl extracted three times with each 300 ml n-BuOH and then washed two times with each 100 ml distilled water. The n-BuOH fraction was dried *in vacuo* and chromatographed over a silica gel column with an eluting solvent consisting of $CHCl_3$-MeOH-H_2O (73:27:10, lower phase). Each fraction was combined according to the result of a TLC check to give **4**, **5**, **6** and **7**. Each compound was identified by physicochemical and spectroscopic methods in a process of comparisons with literature data (Kim et al., 1998; Lee *et al.*, 1991). On co-TLC, these prosapogenins (**4**-**7**) were shown to be present in the MeOH extract, and only two (**5** and **7**) of them were used for the anti-lipid peroxidation test.

4 *(δ-hederin, 65 mg)*: Colorless needles from MeOH, mp 228-230×C, ^{1}H-NMR and ^{13}C-NMR: literature (Kim *et al.*, 1998)

5 *(kalopanaxsaponin A, 1.8 g)*: Colorless needles from MeOH, mp 265-268°C, ^{1}H-NMR and ^{13}C-NMR: literature (Kim *et al.*, 1998)

6 *(kalopanaxsaponin H, 54 mg)*: Colorless needles from MeOH, mp 218-220°C, ^{1}H-NMR and ^{13}C-NMR: literature (Kim *et al.*, 1998)

7 *(kalopanaxsaponin K, 1.2 g)*: Amorphous white powder from MeOH, mp 208-210°C, ^{1}H-NMR and ^{13}C-NMR: literature (Lee *et al.*, 1991)

Animals

Male Sprague-Dawley rats (weighting 150-200 g) were fed *ad libitum* with commercial standard rat diet and water, and maintained at 20 ± 2°C a 12 h light/dark cycle.

Administration of samples and induction of malondialdehyde

Animals were orally administered daily with doses of 250 and 500 mg/kg of several extracts of *Kalopanax pictus*, and were also intraperitoneally injected daily with 10, 20, and 30 μmole/kg of hederagenin monodesmosides and bisdesmosides, for a period of one week. After this, bromobenzene (480 mg/kg) was intraperitoneally injected twice a day for two days and the animals were decapitated 24 h after the final injection. For the other group, the selected compound, kalopanaxsaponin A, was intraperitoneally injected daily at doses of 10, 20, and 30 mg/kg for one week for the induction of hepatic drug-metabolizing enzymes.

Measurement of malondialdehyde

The animals were sacrificed by exsanguination from the abdominal aorta under slightly anesthetic CO_2 gas. The liver was exhaustively perfused with ice-cold normal saline through the portal vein until uniformly pale and weighed. The level/concentration/amount of the thiobarbituric acid (TBA) reactive substance in the liver was measured as a marker of lipid peroxidation by the method of Ohkawa *et al.* (1979). An aliquot (0.4 ml) of 10% liver homogenate in 0.9% NaCl was added to 1.5 ml of 8.1% SDS, 1.5 ml of 20% acetate buffer (pH 3.5) and 1.5 ml of 0.8% TBA solution. The mixture was heated at 95°C for 1 h. After cooling, 5.0 ml of n-butanol:pyridine (15:1) was added for extraction, and the absorbance of the n-butanol:pyridine layer at 532 nm was measured to determine the level/concentration/amount of the TBA reactive substance.

Analytical methods for the measurement of hepatic drug-metabolizing enzymes

Aniline hydroxylase activity (Bidlack *et al.*, 1982) was

assayed by determining p-aminophenol formation from aniline hydrochloride. Epoxide hydrolase activity (Habig *et al.*, 1974) was measured spectrophotometrically by monitoring the rate of *trans*-stilbene oxide (TSO) decrease at 229nm as described previously. Glutathione S-transferase activity (Habig *et al.*, 1974) was assayed by conjugated glutathione 2,4-dinitrobenzene formation from 1-chloro-2,4-dinitrobenzene. For the glutathione content, the reaction mixture consisted of 0.5 ml homogenate and 0.5 ml of 4% sulfosalicylic acid. The mixture was centrifuged at 1,000 × g for 10 min and 0.3 ml of the supernatant was added to 2.7 ml of disulfide reagent. After 20 min at room temperature the absorbance was assessed at 412 nm against a blank of water.

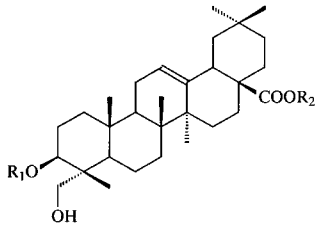
Statistics

The statistical differences between experimental groups were analyzed with the student t-test.

RESULTS AND DISCUSSION

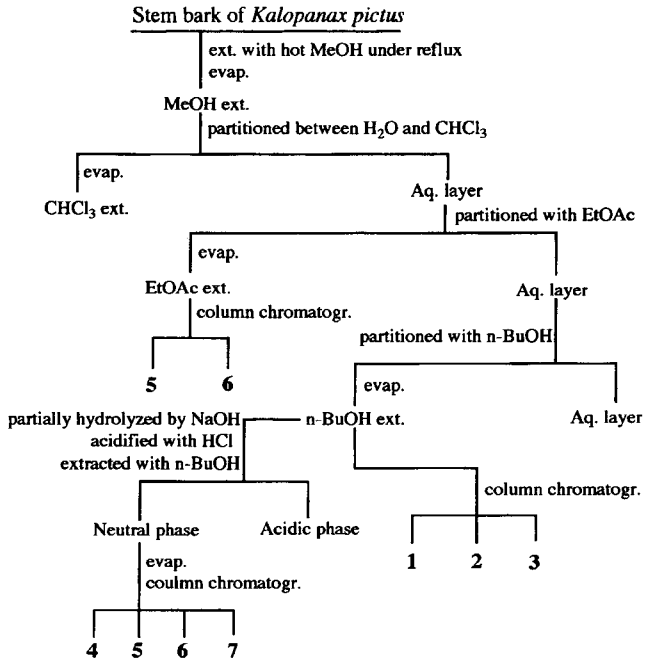
As shown in Scheme 1, the n-BuOH fraction, designated as saponin fraction, mainly contains hederagenin bisdesmosides such as kalopanaxsaponin B, H and K, whereas the EtOAc fraction contains monodesmosides such as kalopanaxsaponin A and -I. In order to obtain large guantities of hederagenin monodesmosides, alkaline hydrolysis of the n-BuOH fraction was conducted and kalopanaxsaponin A and sapindoside C were further isolated by silica gel column chromatography. These two compounds are the monodesmosides of kalopanaxsaponin B and -J, respectively, as shown in Fig. 1.

The treatment of bromobenzene considerably increased the malondialdehyde (MDA) content in the liver of the male rats from 19.8 ± 2.40 nmole/g of tissue for the normal group to 52.8 ± 3.10 nmole/g of tissue for the control group (Table I). The treatment of n-BuOH fraction did not inhibit MDA formation, whereas the treatment of



1: R_1=α-L-rha(*p*) (1→2)-α-L-ara(*p*); R_2=α-L-rha(*p*) (1→2)-β-D-glc (1→6)-β-D-glc(*p*)
2: R_1=β-D-xyl(*p*) (1→3)-α-L-rha(*p*) (1→2)-α-L-ara(*p*); R_2=α-L-rha(*p*) (1→2)-β-D-glc(*p*) (1→6)-β-D-glc(*p*)
3: R_1=β-D-glc(*p*) (1→4)-β-D-xyl(*p*) (1→3)-α-L-rha(*p*) (1→2)-α-L-ara(*p*); R_2=α-L-rha(*p*) (1→2)-β-D-glc(*p*) (1→6)-β-D-glc(*p*)
4: R_1=α-L-rha(*p*); R_2=H
5: R_1=α-L-rha(*p*) (1→2)-α-L-ara(*p*); R_2=H
6: R_1=β-D-xyl(*p*) (1→3)-α-L-rha(*p*) (1→2)-α-L-ara(*p*); R_2=H
7: R_1=β-D-glc(*p*) (1→4)-β-D-xyl(*p*) (1→3)-α-L-rha(*p*) (1→2)-α-L-ara(*p*); R_2=H

Fig. 1. Structures of sapnins isolated from the stem bark of *K. pictus*



Scheme 1. Extraction, fractionation and isolation from the stem bark of *K. pictus*

Table I. Effect of the *K. pictus* stem bark extracts on hepatic lipid peroxide contents in bromobenzene-treated male rats

Group	Dose (mg/kg)	MDA nmole/g of tissue (inhibition %)
Normal		19.8 ± 2.40
Bromobenzene		52.8 ± 3.00[1)]
MeOH extract	250	57.6 ± 2.20 (-14.5)
	500	47.2 ± 1.79* (17.0)
EtOAc fraction	250	43.7 ± 3.00* (27.5)
	500	42.3 ± 3.15** (31.8)
n-BuOH fraction	250	53.3 ± 3.30 (1.5)
	500	60.3 ± 4.30 (22.7)
Hydrolysate fraction[2)]	250	48.7 ± 3.30 (12.4)
	500	42.3 ± 2.50** (31.8)
Ascorbic acid	100	26.8 ± 2.14*** (79.8)

Rats were orally administered with *K. pictus* extract, its fractions and ascorbic acid, daily for one week and then bromobenzene (480 mg/kg, *i.p.*) was injected twice a day at 12 h intervals for two days. Rats were decapitated 24 h after the last injection.
[1)]Values are mean ± S.D. for 6 experiments (5 animals for each experiment). *P<0.05, **P<0.01 and ***P<0.001, compared with the bromobenzene treatment, as analyzed with the T-test by Duncan's multiple range test.
[2)]Hydrolysate fraction means partially hydrolyzed fraction by NaOH.

the alkaline hydrolysate of the n-BuOH fraction markedly decreased the MDA content in an effect demonstrated to be similar to that of the EtOAc fraction-treated group.

Table II. Effect of hederagenin monodesmosides and bisdesmosides isolated from the *K. pictus* stem bark on hepatic lipid peroxide contents in bromobenzene-treated male rats

Group	Dose (μmole/kg)	MDA nmole/g of tissue (inhibition %)
Normal		19.8 ± 2.40
Bromobenzene		52.8 ± 3.00[1)]
Kalopanaxsaponin A	10	37.2 ± 2.69** (47.2)
(**5**)	20	37.3 ± 2.00** (47.0)
	30	35.5 ± 2.40** (52.4)
Kalopanaxsaponin B	10	54.0 ± 3.69 (-3.6)
(**1**)	20	58.9 ± 4.60 (-18.5)
	30	55.0 ± 2.39 (-6.7)
Sapindoside C	10	47.2 ± 3.39* (17.0)
(**7**)	20	41.0 ± 3.00* (35.8)
	30	31.5 ± 3.00*** (64.5)
Kalopanaxsaponin K	10	62.3 ± 5.20 (-28.7)
(**3**)	20	58.0 ± 5.00 (-15.8)
	30	57.2 ± 4.89 (-13.3)
Kalopanaxsaponin H	10	52.9 ± 2.99 (-0.3)
(**2**)	20	51.5 ± 3.20 (3.9)
	30	53.0 ± 2.80 (-0.6)
Ascorbic acid	10 mg/kg	24.6 ± 2.10*** (85.5)

Rats were intraperitoneally administered with saponins isolated from *K. pictus* and ascorbic acid, daily for one week and then bromobenzene (480 mg/kg, *ip*) was injected twice a day at 12 h intervals for two days. Rats were decapitated 24 h after the last injection.
[1)]Values are mean ± S.D. for 6 experiments (5 animals for each experiment).
*P<0.05, **P<0.01 and ***P<0.001, compared with the bromobenzene treatment, as analyzed with the T-test by Duncan's multiple range test.

This suggests the inhibitory activity on MDA formation is derived from hederagenin.

To compare the anti-lipid peroxidation activity between hederagenin monodesmosides and bisdesmosides, we isolated kalopanaxsaponin B, -H and -K from the n-BuOH fraction and also isolated δ-hederin, kalopanaxsaponin A, -I and sapindoside C from alkali hydrolysate. These compounds were identified by comparisons of spectral data with the literature data (Kim *et al.*, 1998; Lee *et al.*, 1991). As shown in Table II, KPS-A and sapindoside C exhibited significant inhibitory effects on MDA formation at 10-30 mmole/kg, and on intraperitoneal administration at 30 mmole/kg they inhibited bromobenzene-induced lipid peroxidation by 53.4% and 64.5%, respectively. In contrast, kalopanaxsaponin B, -H and -K, which are all hederagenin bisdesmosides, demonstrated no activity suggesting that it was the hederagenin monodesmosides that were responsible for anti-lipid peroxidation of kalopanaxsaponins. Saito *et al.* (Saito *et al.*, 1993) have reported that only hederagenin bisdesmosides protect hepatocytes from the damage caused by CCl_4, whereas the metallothionein induction activity of hederagenin monodesmosides has been reported (Iszard *et al.* 1995). We have previously described the antimutagenic activity manifested by hederagenin and its glycosides in the Ames test, irrespective of monodesmosides or bisdesmosides, suggesting that they scavenge electrophilic intermediates that are capable of inducing mutation (Park *et al.* 2000). However, in spite of our expectations, hederagenin bisdesmosides failed to demonstrate anti-lipid peroxidation.

Bromobenzene 3,4-oxide, a metabolite produced from bromobenzene treatment, has been known to induce lipid peroxidation in the liver. This oxide should be converted to bromobenzene 3,4-dihihydrodiol or bromobenzene glutathione by epoxide hydrolase and gluta-

Table III. Effect of kalopanaxsaponin a isolated from *K. pictus* stem bark on hepatic drug-metabolizing enzymes in rats

Group	Normal	Bromoben.	Kalopanaxsaponin A (mg/kg)			Ascorbic acid
(mg/kg)	0	480 (i.p.)	10 (i.p.)	20 (i.p.)	30 (i.p.)	100 (p.o.)
GST.[2)]	213.4 ± 10.56[1)a]	220.9 ± 15.79[a]	204.2 ± 11.33[a]	225.8 ± 16.47[a]	227.9 ± 20.31[a]	230.8 ± 21.67[a]
Glut.[3)]	2.19 ± 0.53[a]	1.86 ± 0.48[a]	2.06 ± 0.55[a]	1.97 ± 0.34[a]	2.07 ± 0.57[a]	2.03 ± 0.39[a]
EH..[4)]	12.45 ± 0.27[a]	5.45 ± 0.30[e]	6.47 ± 0.20[d]	8.23 ± 0.14[c]	8.77 ± 0.28[c]	10.28 ± 0.95[b]
AD[5)]	2.86 ± 0.12[b]	3.47 ± 0.17[a]	3.33 ± 0.15[a]	2.98 ± 0.19[b]	2.95 ± 0.13[b]	2.77 ± 0.11[b]
AH.[6)]	0.63 ± 0.08[c]	0.89 ± 0.04[a]	0.90 ± 0.05[a]	0.84 ± 0.06[a]	0.80 ± 0.07[a]	0.72 ± 0.04[b,c]

Abbreviation: GST (glutathione S-transferase), Glut (glutathione), EH (epoxide hydrolase), AD (aniline m\demethylase), AH (aminopyrine hydroxylase); Rats were intraperitoneally injected daily for seven days and animals were decapitated 24 h after the last injection.
[1)]Vlaues are mean ± S.D. for six experiments. Values with same superscript letter are not significantly different in each row ($p < 0.05$).
[2)]1,2-dinitro-4-nitrobenzene nmol/mg protein/min.
[3)]mmol/g of tissue.
[4)]nmol/g of tissue.
[5)]HCHO nmol/mg protein/min.
[6)]p-aminophenol nmol/mg protein/min.

thione S-transferase, and finally excreted in the urine (Park *et al.*, 1996). As shown in Table III, no statistically significant changes were observed in glutathione S-transferase activity or glutathione content. The aniline hydroxylase activity slightly decreased though not to a statistically significant degree. However, the epoxide hydrolase activity significantly increased whereas the aminopyrine *N*-demethylase activity significantly decreased. The activity levels were comparable to those of potent antioxidant ascorbic acid. The significant changes observed for these two enzymes could represent crucial evidence of the anti-lipid peroxidative potential of KPS-A. Among the tested saponins other effective compounds may also follow the trend of hepatic-drug metabolizing enzyme changes that were demonstrated here in rats treated with KPS-A. The unique physicochemical property of saponins, i.e., their surfactant activity presumably may trigger considerable changes in hepatic drug-metabolizing enzyme activities through a particular biochemical mediation. In conclusion, KPS-A and sapindoside C are at least as responsible for anti-lipid peroxidation as the active principles. Such a degree of activity could explain the antihepatotoxic and anti-diabetic effects of saponins that have already been reported.

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