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Note

# Antibacterial Phenylpropanoid Glycosides from *Paulownia tomentosa* Steud

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The butanol extract of *Paulownia tomentosa* stem showed antibacterial activity against *Staphylococcus aureus* (SG511, 285 and 503), *Streptococcus pyogenes* (A308 and A77) and *Streptococcus faecium* MD8b etc. The most active compound of the extract was identified to be campneoside I, which had a minimal inhibitory concentration(MIC) of 150 μg/ml against *Streptococcus* and *Staphylococcus* species. From such antibacterial activity, the methoxy group of campneoside I was postulated to be the essential element for the antibacterial activity.

**Key words:** *Paulownia tomentosa* Steud, Campneoside I, Campneoside II, Martynoside, Acteoside, Antibacterial activity, Minimum inhibitory concentration, Cytotoxicity

## INTRODUCTION

*Paulownia tomentosa* Steud is a perennial tree which is widely distributed throughout Korea, Japan and China, and has been used as Oriental Medicine (Chinese Drugs Encyclopedia Vol.III, 1985) for the treatment of gonorrhoea, bruise, and erysipelas and deodorant etc.

Several compounds such as catapol and syringin (Yoneiti *et al.*, 1959), aucubin, iridoid glycosides, coniferin, acteoside (Hegnauer *et al.*, 1978; Adriani *et al.*, 1981; Sticher *et al.*, 198) were reported to be found in *Paulownia tomentosa* Steud. Besides these publication, but there are a few reports concerning composition of paulownin, sesamin and (+)-piperitol (Takahashi *et al.*, 1963; Ina *et al.*, 1987) etc.

We searched for the new class of antibacterial agent from natural resources especially from plant materials (Park *et al.*, 1991; Jang *et al.*, 1991; Park *et al.*, 1992; Jang *et al.*, 1993). Through this work, some compounds obtained from butanol extract of *Paulownia tomentosa* stem were screened for the antibacterial activity against a various bacterium, *in vitro*.

## MATERIALS AND METHODS

### Material

The stem of *Paulownia tomentosa* Steud was purchased from a herbal drug dealer in Kyung-Dong Herbal Drug Market in 1990 (Seoul, Korea) and plant identification was confirmed by Dr. Dae S. Han, the professor emeritus of College of Pharmacy, Seoul National University. Voucher speciemens were deposited in our laboratory.

### Reagents

Fetal bovine serum (FBS) and horse serum (HS), Gibco Lab. (Grand Island, NY) and Müller-Hinton agar (MH), Difco were used. All other chemicals and organic solvents were obtained from Sigma Chemical Co. and Duksan Company (Seoul, Korea), respectively.

### Instruments

$^{1}$H-NMR spectra were taken at 200 MHz and $^{13}$C-NMR at 80 MHz using Bruker AM-200, Varian VXR-50000 spectrometer, Jeol JNM-GSX 400 and Bruker FT-80A spectrometer. Mass spectrum (70 eV) were analyzed by direct inlet and recorded by GC-MS QP-100 spectrometer (Shimadzu). Melting points were determined by Gallen Kamp Melting Point Apparatus and uncorrected.

### Extraction and Isolation of Phenylpropanoid Glycosides

Stem of *Paulownia tomentosa* (20 Kg) was extracted three times with 20 liters of methanol for 6 hours to

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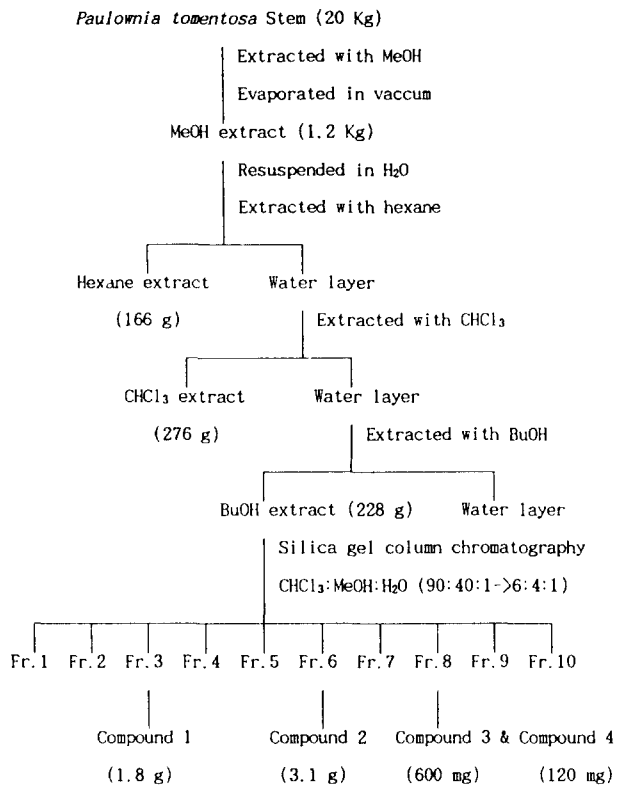



**Fig. 1.** Fractionation scheme of MeOH extract from the stem of *Paulownia tomentosa* Steud.

give a total extract of 1,450 g, which was resuspended in water and extracted three times with equal volume of hexane, to give 166 g of concentrated hexane extract. The water layer was extracted three times with equal volume of chloroform to give 276 g of chloroform extract. The water layer was extracted three times with equal volume of butanol to give 228 g of butanol extract. Butanol extract was allotted into ten fractions (Fr. 1-Fr. 10) using silica gel column chromatography with $CHCl_3$/MeOH/$H_2O$ as gradient elution (See Fig. 1).

**Compound 1:** amorphous powder, $C_{31}H_{40}O_{15}$ (mw: 652), Rf: 0.35 ($CHCl_3$ : MeOH = 3 : 1, Kiselgel 60 F254), IR $\upsilon_{max}^{KBr}$·$cm^{-1}$: 3400, 1710, 1640, 1602, 1520, 1280 and 1040. $[\alpha]_D^{20}$ = 28.2° (C = 0.20, $CHCl_3$), Elemental analysis: C 56.82%, H 6.24% and O 36.94% (calculated for $C_{45}H_{54}O_{22}$·$H_2O$: C 57.06%, H 6.18% and O 36.76%), $^1$H-NMR (200 MHz, $CD_3OD$, δ ppm): 7.68 (1H, d, J = 16 Hz, Ar-CH=C), 6.6-7.2 (total 6 H, aromatic H), 6.40 (1H, d, J = 16 Hz, Ar-C=CH), 3.84 and 3.80 (3 H each, s, 2×$CH_3$), 2.84 (2H, t, J = 7 Hz, Ar-$CH_2$), 1.13 (3H, d, J = 6 Hz, $CH_3$ of rhamnose).

**Compound 2:** amorphous powder, $C_{29}H_{36}O_{15}$ (mw: 624), Rf: 0.40 ($CHCl_3$ : MeOH : $H_2O$ = 6 : 4 : 1, Kiselgel 60 F254), mp: 148-152℃, IR $\upsilon_{max}^{KBr}$·$cm^{-1}$: 3400, 1700, 1640, 1610, 1520, 1280 and 1040. UV $\lambda_{max}^{KBr}$ · nm: 208, 220, 290 and 330. $[\alpha]_D^{20}$ = −73.0° (C = 0.50, MeOH), Elemental analysis: C 55.17%, H 5.83% and O 39.0% (calculated for $C_{29}H_{36}O_{15}$: C 55.77%, H 5.77% and O 38.46%). MS ($EI^+$, 70 eV, m/z, rel.int.): 316 (0.8), 154(37.3), 137(24.6), 136(23.7), 123(28.1) and 110(12.8). $^1$H-NMR (200 MHz, $CD_3OD$, ppm): 7.62 (1H, d, J = 16 Hz, Ar-CH=C), 6.56-7.09 (total 6 H, aromatic H), 6.30 (1H, d, J = 16 Hz, Ar-C=CH), 5.20 (1H, s, H-1 of rhamnose), 4.40 (1H, d, J = 8 Hz, H-1 of glucose), 2.82 (2H, t, J = 7 Hz, Ar-$CH_2$) and 1.14 (3H, d, J = 6 Hz, $CH_3$ of rhamnose).

**Compound 3:** amorphous powder, $C_{30}H_{38}O_{16}$ (mw: 654), Rf: 0.48 ($CHCl_3$ : MeOH : $H_2O$ = 6 : 4 : 1, Kiselgel 60 F254), mp: 142-148℃, IR $\upsilon_{max}^{KBr}$·$cm^{-1}$: 3400, 1700, 1610, 1520, 1450, 1280, 1160 and 1040. UV $\lambda_{max}^{MeOH}$ · nm: 208, 220, 290 and 330. $[\alpha]_D^{20}$ = −72.4° (C = 0.30, MeOH), Elemental analysis: C 55.48%, H 5.89% and O 38.63% (calculated for $C_{30}H_{38}O_{16}$: C 55.05%, H 5.81% and O 39.14%). MS ($EI^+$, 70 eV, m/z, rel.int.): 270(6.4), 176(3.7), 162(21.3), 152(30.4), 137(14.0), 128 (68.4), 123(87.4), 110(100) and 69(71.6), 55(80.5). $^1$H-NMR (200 MHz, $CD_3OD$, ppm): 7.62 (1H, d, J = 16 Hz, Ar-CH=C), 6.75-7.07 (total 6H, aromatic H), 6.28 (1H, d, J = 16 Hz, Ar-C=CH), 5.22 (1H, s, H-1 of rhamnose), 4.43 (1H, d, J = 8 Hz, H-1 of glucose) and 1.11 (3H, d, $CH_3$ of rhamnose).

**Compound 4:** amorphous powder, $C_{29}H_{36}O_{16}$ (mw: 640), Rf: 0.21 ($CHCl_3$ : MeOH : $H_2O$ = 6 : 4 : 1, Kiselgel 60 F254), mp: 178-183℃, IR $\upsilon_{max}^{KBr}$·$cm^{-1}$: 3400, 1700, 1605, 1510, 1450, 1280, 1160 and 1040. UV $\lambda_{max}^{MeOH}$ · $cm^{-1}$: 208, 220, 290 and 330. $[\alpha]_D^{20}$ = −55.6° (C = 0.25, MeOH), Elemental analysis: C 53.82%, H 5.72% and O 40.46% (calculated for $C_{29}H_{36}O_{16}$: C 54.38%, H 5.63% and O 39.99%). MS ($EI^+$, 70 eV, m/z, rel.int.): 136(3.7), 128(25.8), 110(100), 98(10.6), 73(33.6), 69(65.6) and 57(91.1). $^1$H-NMR (200 MHz, $CD_3OD$, ppm): 7.61 (1H, d, J = 16 Hz, Ar-CH=C), 6.73-7.08 (total 6H, aromatic H), 6.28 (1H, d, J = 16 Hz, Ar-C=CH), 5.22 (1H, s, H-1 of rhamnose), 4.40 (1H, d, J = 8 Hz, H-1 of glucose) and 1.11 (3H, d, J = 6 Hz, $CH_3$ of rhamnose).

### *In vitro* Evaluation of Antibacterial Activity

Antibacterial activity was examined with agar plate dilution method on Müller-Hinton (MH) agar plate and the minimum inhibitory concentration (MIC) was determined using five Escherichia, four *Pseudomonas*, one *Salmonella*, two *Klebsiella*, two *Enterobacter*, three *Streptococcus* and three *Staphylococcus* species.

For the activation of the bacterial strains, they were cultured at 37℃ for 18 hrs on MH agar slant and then on MH liquid medium for 18 hrs. Sheep red

blood cells (10%) and horse serum (10%) were added to the media for *Streptococcus species*. To determine MIC values, each test materials were added to MH agar plate and then 1 ml of bacterial solutions (about $1\times10^6$ cells) were smeared on the agar plates using Cathra System (MCT Medical No. 2.00). To dissolve test compounds, they were dissolved in 15 ml of 0.1 N-NaOH and then serially diluted with MH medium.

The MIC values of the test materials were determined by comparing the degree of the bacterial cell growth on the serially diluted culture plate with cifroxacin as the positive control after at 37℃ for 18 hrs. (Bae *et al.*, 1990; Seo *et al.*, 1986; Namba *et al.*, 1981).

### Cytotoxicity of Phenylpropanoid Glycosides

To measure the *in vitro* cytotoxity of martynoside, acteoside and campneoside I which have phenylpropanoid glycosides moieties on the mouse leukemia cell lines, L1210 and P388, MTT determination method of a modified Mossman method (James *et al.*, 1987) was used. Briefly, the cells were cultured under the conditions of 10% $CO_2$ and 100% relative humidity by using R10 medium which contains 90% RPMI 1640, 10% fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin sodium and 100 mg/ml streptomycin sulfate. Adriamycin was used as positive control. After dissolving test compounds in MeOH, they were further diluted with R10 medium.

Throughout the experiment, the drug-exposure time was 48 hours and the cell concentration was 5,000 cells/well. $IC_{50}$ were the concentration of which their absorbance half of the absorbance value of the untreated control well:

$$\frac{OD_{540}\text{ of test well} - OD_{540}\text{ of background well}}{OD_{540}\text{ of control well} - OD_{540}\text{ of background well}} \times 100$$

($OD_{540}$: mean optical density at 540 nm)

## RESULTS AND DISCUSSION

### Isolation and Identification of Phenylpropanoid Glycosides

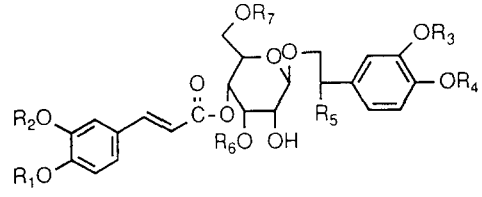
As shown in Fig. 1, the isolation process of active compounds was monitored by HPLC. Butanol fraction was applied on silica gel column using gradient solvent system, $CHCl_3$ : MeOH : $H_2O$ (from 90 : 40 : 1 to 6 : 4 : 1) to give compound 1 (1.8 g), compound 2 (3.1 g), compound 3 (600 mg) and compound 4 (120 mg).

UV spectrum of compound 1 showed specific absorption bands of phenylpropanoid glycoside at 220, 290 and 330 nm. IR spectrum of it showed double bonds of aromatic ring at 1640, 1602 and 1520 $cm^{-1}$ and C-O bond at 1000-1100 $cm^{-1}$. Its $^1$H-NMR spectrum showed trans olefinic protons at δ 6.40 and 7.68 ppm (each 1H, d, J=16 Hz), 5.21 ppm (1H, s, anomeric proton of rhamnose), 4.42 ppm (1H, d, J=8 Hz, anomeric proton of glucose), 2.84 ppm (2H, t, J=7 Hz Ar-$CH_2$) and 1.13 ppm (3H, d, J=6 Hz, $CH_3$ of rhamnose). Instrumental analysis data coincided with their reference figures (Sasaki *et al.*, 1978; Sasaki *et al.*, 1989; Andary *et al.*, 1982). Compound 1 was identified as 2-(3′-hydroxy-4-methoxyphenyl)-ethanol-1-O-α-L-rhamnosyl(1→3)-(4-feruloyl)-β-D-glucoside (=Martynoside).

IR spectrum of compound 2 showed C=O group (1700 $cm^{-1}$) and aromatic double bonds at 1640, 1610 and 1520 $cm^{-1}$. Its $^1$H-NMR spectrum showed trans olefinic protons at δ 6.30 and 7.62 ppm (each 1H, d, J=16 Hz), 5.20 (1H, s, Ar-H of rhamnose), 4.40 ppm (1H, d, J=8 Hz, anomeric proton of glucose), 2.82 ppm (2H, t, J=7 Hz, $CH_2$) and 1.14 ppm (3H, d, J=6 Hz, $CH_3$ of rhamnose). Instrumental analysis data coincided with their reference figures (Sasaki *et al.*, 1989; Andary *et al.*, 1982; Miyase *et al.*, 1982; Gering *et al.*, 1987; Kobayashi *et al.*, 1987; Kitagawa *et al.*, 1984). Compound 2 was identified as β-(3,4′-dihydroxyphenyl)-ethyl-O-α-L-rhamnopyranosyl(1→3)-β-D-(4-O-caffeoyl)-glucopyranoside (=Acteoside).

IR spectrum of compound 3 showed C=O group (1700 $cm^{-1}$) and aromatic double bonds at 1610, 1500 and 1450 $cm^{-1}$. Its $^1$H-NMR spectrum showed trans olefinic protons at δ 7.62 ppm (each 1H, d, J=16 Hz, Ar-CH=C), 6.75-7.07 ppm(total 6H, Ar-H), 6.28 ppm (1H, d, J=16 Hz, Ar-C=CH), 5.22 ppm (1H, s, H-1 of rhamnose), 4.43 (1H, d, J=8 Hz, H-1 of glucose) and 1.11 ppm (3H, d, $CH_3$ of rhamnose). Instrumental analysis data coincided with their reference figures (Andary *et al.*, 1982; Imakura *et al.*, 1985). Compound 3 was identified as R,S-β-hydroxy-β-(3′,4′-dihydroxyphenyl)-ethyl-O-α-L-rhamno-pyranosyl(1→3)-β-D-(4-O-caffeoyl)-glucopyranoside (=Campneoside I).

IR spectrum of compound 4 showed OH group (3400 $cm^{-1}$), C=O group (1700 $cm^{-1}$) and aromatic double bonds at 1605, 1510 and 1450 $cm^{-1}$. Its $^1$H-




| Compounds | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ |
|---|---|---|---|---|---|---|---|
| Martynoside | H | $OCH_3$ | H | $OCH_3$ | H | rhamnosyl | H |
| Acteoside | H | H | H | H | H | rhamnosyl | H |
| Campneoside I | H | H | H | H | $OCH_3$ | rhamnosyl | H |
| Campneoside II | H | H | H | H | OH | rhamnosyl | H |

**Fig. 2.** Chemical structures of phenylpropanoid glycosides.

NMR spectrum showed secondary methyl group (3H, d, J=6 Hz) at δ 1.11 ppm, anomeric proton (1H, d, J=8 Hz) of glucose at δ 4.40 ppm, anomeric proton (1H, s) of rhamnose at δ 5.22, olefinic proton (each 1H, d, J=16 Hz) of AB type at δ 6.28 and 7.61 ppm, aromatic proton (total 6H) at δ 6.73-7.08 ppm. Instrumental analysis data were coincided with those of its reference figure (Kitagawa *et al.*, 1984; Imakura *et al.*, 1985; Kitagawa *et al.*, 1987). Compound 4 was identified as R,S-β-(3',4-dihydroxyphenyl)-ethyl-O-α-L-rhamno pyranosyl(1→3)-β-D-(4-O-caffeoyl)-glucopyranoside(=β-hydroxyacteoside, Campneoside II).

Also, we could identify the β-binding form from the doublet coupling (J=8 Hz) of anomeric proton peak of glucose and the α-binding form from the singlet of anomeric proton of rhamnose (Andary *et al.*, 1982).

From the results obtained above, compound 1, 2, 3 and 4 were identified as martynoside, acteoside, campneoside I and II, respectively (See Fig. 2).

## Antibacterial Activity of Martynoside, Acteoside and Campneoside I

Comparing the antibacterial activities of acteoside and campneoside I (MIC, 150 μg/ml) isolated from the stem of *Paulownia tomentosa*, campneoside I was more potent than acteoside (Kitagawa, S. *et al.*, 1987; Shoyama, Y. *et al.*, 1987) (See Table I).

As shown in Table II, campneoside I, β-hydroxyacteoside (campneoside II), forsythiaside and suspensaside, derivatives of acteoside, showed antibacterial activity (Kitagawa, S. *et al.*, 1987), but no activity was observed from martynoside and also another derivative of it. Especially, the presence of R5, R6 and R7 group in the structure of phenylpropanoid glycoside as shown in Fig 2 was determined to be the essential functional groups for antibacterial activity. According to the MIC values of phenylpropanoid glycoside against *Staphylococcus aureus*, when H radical were positioned at R1, R2, R3 and R4 with the presence of rhamnosyl radical at position R6 conferred on a stronger activity than when at position R7. At position R5, the presence of $CH_3O$ showed the strongest antibacterial activity, that of OH showed medium activity and that of H showed the weakest activity, i.e., Rhamnosyl: R6>R7, R5: $CH_3O$>OH>H.

## Cytotoxicity of Phenylpropanoid Glycosides

Cytotoxicities($IC_{50}$) of martynoside and acteoside

**Table II.** Antibacterial activity of phenylpropanoid glycoside against *Staphylococcus aureus*

| Compounds | MIC |
|---|---|
| Suspensaside | 4.1 mM (2.6 mg/ml) |
| Forsythiaside | 3.2 mM (2.0 mg/ml) |
| Acteoside | 3.2 mM (2.0 mg/ml) |
| Campneoside II | 2.0 mM (1.3 mg/ml) |
| Campneoside I | 0.2 mM (0.15 mg/ml) |

**Table I.** Antibacterial activity of phenylpropanoid glycoside

| Bacterial Strain | MIC (μg/ml) of Comp. 1 | Comp. 2 | Comp. 3 | Cifroxacin |
|---|---|---|---|---|
| *Streptococcus pyogenes* A308 | >2,100 | 750 | 150 | 1.563 |
| *Streptococcus pyogenes* A77 | >2,100 | 1,500 | 150 | 1.563 |
| *Streptococcus faecium* MD8b | >2,100 | 3,000 | 150 | 0.781 |
| *Staphylococcus aureus* SG511 | >2,100 | 375 | 150 | 0.781 |
| *Staphylococcus aureus* 285 | >2,100 | 375 | 150 | 0.781 |
| *Staphylococcus aureus* 503 | 1,050 | 375 | 150 | 0.781 |
| *Escherichia coli* O 55 | >2,100 | 3,000 | >600 | 0.025 |
| *Escherichia coli* DC O | >2,100 | 3,000 | >600 | 0.195 |
| *Escherichia coli* DC 2 | >2,100 | 750 | >600 | 0.195 |
| *Escherichia coli* TEM | 2,100 | 3,000 | >600 | 0.013 |
| *Escherichia coli* 507E | 2,100 | 3,000 | >600 | 0.025 |
| *Pseudomonas aeruginosa* 9027 | >2,100 | 750 | >600 | 0.391 |
| *Pseudomonas aeruginosa* 1592E | >2,100 | 1,500 | >600 | 0.391 |
| *Pseudomonas aeruginosa* 1771 | >2,100 | 1,500 | >600 | 0.391 |
| *Pseudomonas aeruginosa* 1771E | >2,100 | 750 | >600 | 0.195 |
| *Salmonella typhimurium* | 1,050 | 3,000 | >600 | 0.013 |
| *Klebsiella oxytosa* 1082E | 1,050 | 750 | >600 | 0.013 |
| *Klebsiella aerogenes* 1522E | >2,100 | 1,500 | >600 | 0.025 |
| *Enterobacter cloacae* P99 | 2,100 | 750 | >600 | 0.025 |
| *Enterobacter cloacae* 1321E | 1,050 | 750 | >600 | 0.007 |

*Comp. 1: martynoside, Comp. 2: acteoside, and Comp. 3: campneoside I

against *in vitro* L1210 and P388 mouse leukemia cell lines tests were 593 μg/ml, 503 μg/ml and 20 μg/ml, 21 μg/ml, respectively. Such a cytotoxicity of acteoside was stronger than that of martynoside to L1210 and P388.

## CONCLUSIONS

1. The active antibacterial compound of *Paulownia tomentosa* stem against *Strep. pyogenes* A308, A77, *Strep. faecium* MD8b, Strep. aureus 285 and 503 was identified as campneoside I. The minimal inhibitory concentration values of the campneoside I were 150 μg/ml for above strains.

2. Cytotoxicity of martynoside was weaker than that of acteoside to L1210 and P388 mouse leukemia cell lines. Furthermore no antibacterial activity was observed for martynoside.

3. The R5 and R6 group in the structure of phenylpropanoid glycoside were the essential elements for the antibacterial activity.

## ACKNOWLEDGEMENTS

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