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Bioactive phenolic compounds in traditional medicines

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Abstract: Bioactive phenolic compounds in traditional medicines were investigated. Arctigenin, matairesinol, trachelogenin and nortrachelogenin from Caulis Trachelospermi, mauritianin from Herba Catharanthi, plantamajoside, acteoside and plantaginin from Plantago Herb, suspensaside, forsythiaside and (+)-pinoresinol O-β-D-glucoside from Forsythia Fruit, and (+)-syringaresinol di-O-β-D-glucoside from Eleutherococcus, were respectively isolated and subjected to assays for their biological activities.

INTRODUCTION

Many kinds of traditional medicines have been used over a long period of time in Asia. However, the active principles in traditional medicines are still unknown. In order to realize the full potential of these medicines, it is important to isolate the specific compounds and to identify the chief active principles in them. Proof of their biological activities must also be elaborated. This article summarizes the research-works on phenolic compounds isolated from several traditional medicines and assays of their biological activities (enzyme inhibitory activities, anti-tumor promoting activity and inhibitory activity of superoxide production *etc*) to identify the bioactive compounds, which were carried out by the author and his collaborators.

The traditional medicines investigated are Caulis Trachelospermi used as an anti-bronchitic agent, an anti-rheumatic and an anti-cancer medicine in China, Herba Catharanthi as an anti-diabetes and an anti-cancer medicine, Plantago Herb as an anti-inflammatory and an anti-allergic medicine in Asia and Europe, Forsythia Fruit as an anti-inflammatory and a diuretic medicine in Asia, and Eleutherococcus (Siberian Ginseng) as a tonic medicine for the nonspecific enhancement of endurance.

CAULIS TRACHELOSPERMI

The origin of the traditional medicine is from *Trachelospermum jasminoides* (Lindli) Lem. (Apocynaceae).

The lignans, arctigenin (1), matairesinol (2), trachelogenin (5) and nortrachelogenin (6), were isolated with their glucosides, arctiin (3), matairesinoside (4), tracheloside (7) and nortracheloside (8), and their structures were elucidated on the basis of chemical and spectral (IR, UV, MS, CD, ^{1}H-NMR and ^{13}C-NMR) evidence, respectively (1).

For the last decade Ca^{2+} antagonists have been used as therapeutic agents, particulary to treat

coronary heart diseases and hypertension.
The lignans isolated were subjected to Ca^{2+} antagonist assay. It was demonstrated that 5 has the most potent inhibitory activity [IC_{50} (x 10^{-5} M) 0.11] and shows a highly potent and relatively long-lasting antihypertensive effect on spontaneously hypertensive rats (2).
Compounds 1, 2, 5 and 6 showed a relaxation effect on histamine-induced contraction of tracheal muscles in the guinea pig, which may be responsible for the therapeutic effect as an anti-bronchitic agent (1).
Compounds 1 and 6 strongly inhibited the superoxide production [IC_{50} (x 10^{-6} M) 3 and 8], which have some correlation with rheumatic disease (1). In addition, the superoxide production has some correlation with cancer disease as a promoter in the two-stage carcinogenesis. Actually, it was reported that 6 has a strong anti-tumor promoting activity (3).
The glucosides, 3, 4, 7 and 8 show no activities. However, it was demonstrated that these glucosides are easily converted to their aglycones by gastrointestinal flora when they are orally administered to rats (4). This suggests the glucosides may act as a kind of pro-drug.

HERBA CATHARANTHI

The origin of the traditional medicine is from *Catharanthus roseus* (L.) G. Bon (=*Vinca rosea* L.) (Apocynaceae).
The anti-cancer alkaloids from this Herb, vinblastine and vincristine, are well known and used as a therapeutic agent for leukemia.
A flavonoid, mauritianin [kaempferol 3-(O-rhamnosyl-(1→2)-O-rhamnosyl-(1→6)-galactoside] (9), was isolated.
The two-stage carcinogenesis consists of the stages of initiation and promotion. It is important to prevent the two-stage carcinogenesis by suppressing the promotion. The screening assay for inhibitors of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema reflects the anti-tumor promoting effect in two-stage carcinogenesis (5).
Compound 9 was tested for the ability to reduce the intensity of TPA-induced ear edema and was shown to have an inhibitory activity. Moreover, 9 enhanced TPA-suppressed delayed-type hypersensitivity (DTH) reaction in mice (6), indicating that 9 augmented the immune resistance to cancer and suppressed the growth of tumors caused by a second inoculation of Ehrlich carcinoma cells (7). These results show that 9 may be an interesting and useful compound for cancer treatment.

PLANTAGO HERB

The four *Plantago* species (Plantaginaceae) are used as the origin of the traditional medicine, that is, *Plantago asiatica* L. and *P. depressa* Willd. in Asia, and *P. major* L. and *P. lanceolata* L. in Europe.
Phenylethanoids, plantamajoside (10), hellicoside (11) and acteoside (12) and flavonoids, plantaginin (15) and 6-hydroxyluteolin 7-glucoside (16), from Herbs of *P. asiatica* and *P. major*, and phenylethanoids, 12, β-hydroxyacteoside (13) and orobanchoside (14), from Herbs of *P. depressa* and *P. lanceolata* were respectively isolated with several minor phenylethanoids (8).
THe structure of 14 was established as structure 14 on the basis of ^{13}C-NMR and X-ray analysis.

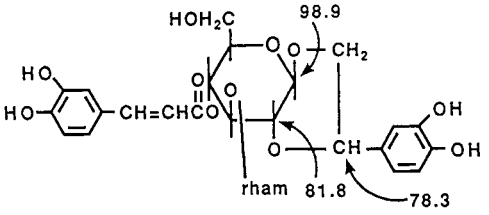

Chart 1. ^{13}C-Shifts in orobanchoside (14)

TABLE 1. Inhibition of phenolic compounds applied topically on arachidonic acid-induced mouse ear edema

	Dose (mg/ear)	Increase of ear thichness ($\times 10^{-2}$mm) Control	Treated	Inhibition (%)
Plantamajoside(10)	1	29.0 ± 1.5	24.4 ± 1.5 (n=6)	12
	3	30.3 ± 1.1	22.6 ± 0.7[b] (n=7)	25
Acteoside(12)	1	31.1 ± 1.6	29.2 ± 1.2 (n=6)	6
	3	29.4 ± 1.5	25.2 ± 0.5[a] (n=7)	14
Plantaginin(15)	1	30.8 ± 1.4	26.8 ± 1.2[a] (n=6)	13

Each value represents the mean ± S.E.
Significantly different from the control, a) P<0.05, b) P<0.01.

It is known that cyclic AMP inhibits the release of a chemical mediator from the mast cell. So when cyclic AMP phosphodiesterase is inhibited by some inhibitor, the concentration of cyclic AMP is increased to inhibit the release of the chemical mediator from the mast cell. Inhibitors against cyclic AMP phosphodiesterase may be useful in the therapy for allergic diseases. In addition, by the presence of 5-lipoxygenase, free arachidonic acid is converted to leukotrienes, which is one of the chemical mediators known as a slow reacting substance of anaphylaxis. Therefore, specific inhibitors of 5-lipoxygenase may be useful in the therapy for allergic diseases.

Compounds 10, 11 and 15 showed a high inhibitory activity against beef heart cyclic AMP phosphodiesterase [IC_{50} (X 10^{-5} M) 16.0, 16.9 and 1.4] and a high inhibitory activity against 5-lipoxygenase from RBL-1 cells [IC_{50} (X 10^{-7} M) 3.73, 3.16 and 1.20] than 12 and 13. Anti-allergic effect of 15 on preconvulsion time caused by spraying antigen-aerosol to sensitized guinea pig with egg albumin was examined to show a significant anti-allergic effect at the 7th day after 50 mg/kg of 15 was intraperioneally administered daily to sensitized guinea pigs. Compounds 10, 12 and 15 showed inhibitory effect on arachidonic acid-induced mouse ear edema (Table 1). Compounds 15 and 16 act as potent inhibitors of HIV reverse transcriptase and showed higher inhibitory activities than baicalin, a well known inhibitor (9).

FORSYTHIA FRUIT

Three *Forsythia* species (Oleaceae) are used as the origin of the traditional medicine, that is, *Forsythia suspensa* Vahl in China, and *F. suspensa*, *F. viridissima* Lindley and *F. koreana* Nakai in Japan and Korea.

Phenylethanoids, forsythiaside (17) and suspensaside (18), and lignans, phillyrin (19) and (+)-pinoresinol O-β-D-glucoside (20) from fruits of *F. suspensa* and *F. koreana*, and phenylethanoids, 12 and 13, and lignans, 3 and 4 from fruits of *F. viridissima* and *F. koreana* were respectively isolated (10).

Compounds 17, 18 and 20 showed a high inhibitory activity against cyclic AMP phosphodiesterase [IC_{50} (X 10^{-5} M) 11.0, 18.3 and 14.2] and IC_{50} of the others was over 50 x 10^{-5} M. Also compounds 17 and 18 showed a high inhibitory activity against 5-lipoxygenase [IC_{50} (X 10^{-7} M) 2.50 and 7.97]. Compound 20 showed an inhibitory effect on histamine release from mast cells induced by concanavallin A [IC_{50} (X 10^{-3} M) 0.2].

Compounds 17, 18 and 20 may be the components responsible for the anti-allergic and anti-inflammatory effects. In addition, 12 has recently been known to have antinephritic and immunosuppressive effects (11).

ELEUTHEROCOCCUS

The Origin of the traditional medicine is from *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (Araliaceae).

Lignan, (+)-syringaresinol di-O-β-D-glucoside (21) was isolated with diglucosides of (+)-medioresinol and (+)-pinoresinol (12).

Compound 21 showed a high inhibitory activity against cyclic AMP phosphodiesterase [IC_{50} (X 10^{-5} M) 12.7]. It is reported that a considerable number of therapeutic agents such as antipsychotics, antianxiety and antihypertensive drugs *etc.* showed inhibitory activity against cyclic AMP phosphodiesterase *in vitro* (13). Therefore, the pharmacological effect of 21 as a tonic as well as antianxiety principles was expected. The effect on exercise time to the point of exhaustion in the chronic swimming stressed rats was examined and it was shown that 21 had a significant and prolonged effect. In the case of restrained cold water stressed rats, 21 displayed an anti-gastric ulcer effect. These results indicate 21 is one component responsible for the pharmacological effect of Eleutherococcus.

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