Arch. Pharm. Res. 3(2), 79~84(1980)

A Survey of the Action of Korean *Angelica* Plants on Drug Metabolism*

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(Received 5 June 1980)

Abstract□ Eight species of the genus *Angelica* in Korea were examined for the activity of affecting drug metabolism and for the presence of coumarins. The results showed that various parts, especially roots and fruits of *Angelica* plants had strong effects on drug metabolism and that they contained various derivatives of coumarins.

Keywords□ *Angelica* plants. Hexobarbital hypnosis. Inhibition and induction of drug metabolizing enzyme. Natural coumarins.

The genus *Angelica* is a large and circumboreal genus, probably to be excluded from the southern hemisphere, and is by far the largest genus of *Umbelliferae* in the Korean flora. Approximately 20 species of the genus *Angelica* are found in Korea. The genus *Angelica* is stout and fistulous or slender, usually erect, herbaceous, caulescent, glabrous to tomentous perennials from stout taproots. Leaves are petioled, membraneous to thick and subcoriaceous ternately-pinnately or pinnately compound;leaflets are broad or narrow, distinct or confluent, dentate, lobed or less commonly dissected; petiols are sheathing; flowers are white, pink, purplish or violet and arranged in compound umbers; fruit is oblong-oval to robicular, strongly flattened dorsally, glabrous to tomentous. Among them, three species are reputed for medicinal use.

In the course of evaluation of Korean medicinal plants for their inhibitory and/or inducing efficacies on drug metabolizing enzymes, it was found that the roots of *Angelica* plants such as *Angelica dahurica, A. gigas* and *A.koreana* exhibited the most potent activity[1,2].

In this communication, we report the results of further screening on various parts of *Angelica* plants which were collected in Korea.

MATERIALS AND METHODS

The plants for this study were collected on Mt. Buk-Han near Seoul and Mt. Gye-Ryong located in the southern part of Korean Penninsula and were botanically identified. The plants were divided into various parts of root, stem, leaf or fruit and were dried in the open air.

The dried parts were cut into small pieces and were extracted with 95% methanol and concentrated.

*Part 3 in the series : Studies on crude drugs acting on drug metabolizing enzymes.

Table I: Effects of *Angelica* plants on hexobarbital-induced hypnosis in mice

Plant name	Plant part	Prolongation		Shortening	
		Dose (mg/kg)	Percent of control	Dose (mg/kg)	Percent of control
Angelica sp. (Mulkangwhal)	root	500	563.6 ($p<0.001$)[a]	250	63.9 ($p<0.02$)
	fruit	500	690.7 ($p<0.001$)	250	76.3 ($p<0.05$)
A. purpuraefolia	root	500	303.0 ($p<0.001$)	250	62.8 ($p<0.01$)
	fruit	500	377.1 ($p<0.001$)	250	69.4 ($p<0.001$)
A. acutiloba	root	500	751.7 ($p<0.001$)	250	85.9 (N. S.)
	fruit	500	816.9 ($0<0.001$)	250	77.4 (N. S.)
A. dahurica	root	250	633.6 ($p<0.0001$)	250	58.0 ($p<0.01$)
	leaf	500	139.0 (N. S.)	250	117.3 (N. S.)
	stem	500	187.9 ($p<0.001$)	250	86.8 (N. S.)
	fruit	500	1009.3 ($p<0.0001$)	250	86.4 (N. S.)
A. decursiva	root	500	321.4 ($0<0.001$)	250	66.3 ($p<0.05$)
	leaf	500	158.9 ($p<0.05$)	250	83.1 (N. S.)
	stem	500	186.7 ($p<0.05$)	250	129.4 (N. S.)
	fruit	250	306.0 ($p<0.001$)	250	111.4 (N. S.)
A. migueliana	root	500	197.6 ($p<0.01$)	250	67.4 ($p<0.05$)
	leaf	500	129.4 (N. S.)	250	78.2 (N. S.)
	stem	500	495.1 ($p<0.01$)	250	96.1 (N. S.)
	fruit	500	125 3 (N. S.)	250	97.5 (N. S.)
A. czernervia	root	500	111.9 (N. S.)	250	92.4 (N. S.)
	leaf	500	164.5 ($p<0.02$)	250	116.5) (N. S.)
	stem	500	122.5 ($p<0.05$)	250	104.9 (N. S.)
A. tenuissima	root	500	181.4 ($p<0.001$)	250	94.5 (N. S.)

a) Student *t*-test.

The indicated amounts of the methanol extracts suspended in 0.5% CMC were administered intraperitoneally. The potency of plant extracts on the inhibition or induction of drug metabolizing enzymes was evaluated according to the alteration of hexobarbital-induced sleeping time in mice. The details of the testing procedures adopted were previously described[1].

RESULTS AND DISCUSSION

The results for the alterations of barbiturate-induced hypnosis in mice by the various different parts of *Angelica* plants were tabulated in Table I. Among eight plants tested, the roots and fruits of Mulkangwhal (*Angelica* spp., not identified) and *A. purpuraefolia* showed not only significant prolongation of barbiturate-induced hypnosis in the enzyme inhibition test, but also significant shortening in the enzyme induction test.

The roots of *A. dahurica, A. decursiva,* and *A. miqueliana* also showed significant activity in both testing system. The other plant parts gave only prolongation of sleeping times; the extracts from the stems and leaves exhibited relatively low activity compared to those of fruits and roots except for stem of *A. miqueliana* which showed rather

Table II: The coumarins in *Angelica* plants

Plant name	Plant part	Coumarins identified	Other main TLC spots unidentified(fluorescence) (R*f* value)	Coumarins reported in the literature
Angelica koreana	root	imperatorin isoimperatorin oxypeucedanin oxypeucedanin-hydrate prangolarin	3(0.34(Bl), 0.11(Bl), 0.05(Y))	imperatorin[13] isoimperatorin[13] oxypeucedanin[13] prangolarin[13] osthol[20]
A. gigas	root	decursin decursinol	3(0.44(Bl), 0.13(Bl), 0.07(Bl))	decursin[14, 15] decursidin[14] decursinol[14, 15] nodakenin[19] umbelliferon[19] nodakenetin[19] imperatorin[21]
Angelica spp. (Mulkangwhal)	root		4(0.52(Bl), 0.22(Bl), 0.07(Bl), 0.14(Bl))	
	fruit	decursinol(?)	6(0.52(Bl), 0.41(Bl), 0.31(Bl), 0.28(Bl) 0.22(Bl), 0.14(Bl))	
A. purpuraefolium	root	decursinol	5(0.6(Bl) 0.48(Bl), 0.39(Bl), 0.2 (Bl), 0.17(Bl))	khellactone[5]
	fruit		4(0.6(Bl), 0.48(Bl), 0.39(Bl), 0.2(Bl))	
A. acutiloba	root	bergapten isoimperatorin	2(0.48(Bl), 0.43(Bl))	bergapten[11]
	fruit	bergapten	2(0.48(Bl), 0.43(Bl))	bergapten[11]

Plant name	Plant part	Coumarins identified	Other main TLC spots unidentified(fluorescence) (R*f* value)	Coumarins reported in the literature
A. dahurica	root	oxypeucedanin-hydrate decursinol prangolarin isoimperatorin imperatorin oxypeucedanin	5(0.40(Y), 0.34(Bl), 0.23(Y), 0.12(PY) 0.07(Bl))	phellopterin[5,6] byakangelicin[5,6] byakangelicol[5,6] oxypeucedanin[6] imperatorin[6] isoimperatorin[6] xanthotoxin[6] marmesin[6] scopoletin[6] anhydrobyakangelicin[6] neobyakangelicin[6] alloisoimperatorin[6]
	leaf		2(0.47(Bl), 0.27(Bl))	
	stem	decursinol	3(0.47(Bl), 0.35(Bl), 0.27(Bl))	
	fruit	imperatorin decursinol	2(0.35(Bl), 0.27(Bl))	byak-angelicin,[12] imperatorin[12] phellopterin[12]
A. decursiva	root	decursin decursinol	4(0.69(Bl), 0.62(Bl), 0.39(Y)) 0.03(B))	umbelliferon,[5] decursin[5,7] decursidin[5,7] nodakenin[8] nodakenetin[5,16] andelin[17] methyl decursinol[7] AD-II[18]
	leaf	decursinol	1(0.39(Bl))	
	stem	decursin	3(0.69(Bl), 0.62(Bl), 0.39(Bl))	
	fruit	bergapten decursin	5(0.69(Bl), 0.62(YBr), 0.39(Bl), 0.3(YBr), 0.03(Bl))	isoimperatorin[9,10] bergapten[9,10] imperatorin[9,10] umbelliferon[9] (+)Hydroxypeucedanin[10]
A. miqueliana	root	decursinol	5(0.66(Bl), 0.56(Bl), 0.42(Bl), 0.29(Bl), 0.11(Bl))	
	leaf	decursinol	2(0.42(Bl), 0.03(Bl))	
	stem	decursinol	2(0.66(Bl), 0.42(Bl))	
	fruit	decursinol	3(0.66(Bl), 0.42(Bl), 0.31(YBr))	
A. czernervia	root	decursin decursinol	4(0.48(Bl), 0.42(Bl), 0.4(Bl), 0.04(Bl))	
	leaf	decursinol decursin	4(0.66(Bl), 0.48(Bl), 0.4(Bl), 0.04(Bl))	
	stem	decursinol	4(0.65(Bl), 0.48(Bl), 0.4(Bl), 0.04(Bl))	
A. tenuissima	root		3(0.54(Bl), 0.31(Bl), 0.28(YBr))	

Developer: toluene: ethylformate: formic acid (5 : 4: 1)

Detection : UV-ray(fluorescence); Bl, blue; Y, yellow; PY, pale yellow; YBr, yellow brown.

strong activity. All extracts from fruits except that from *A. miqueliana* produced very strong activity.

It has been demonstrated that some coumarin derivatives (mainly synthetic) with repeated administrations of them to mice, exhibited significant inducing activity on drug metabolizing enzymes as measured by barbiturate-induced sleeping time[3].

Systematic chemical fractionation and pharmacological studies on the roots of *A. koreana* recently showed that the activity was attributed to natural furanocoumarins[4].

And moreover, it is generally accepted that major constituents of *Angelica* plants are coumarins (Table II).

We, made therefore, an attempt to identify the presence of coumarins in *Angelica* plants by co-TLC with authentic samples such as furano, pyrano and simple coumarins in order to find out whether there is any strict relationship between the number and sorts of coumarins in *Angelica* plants and their biological activity.

As shown in Tables I and II, significant activities produced by the roots and fruits of *Angelica acutiloba* as well as *A. dahurica* and also by the roots of *A. koreana*[4] were readily attributable to furanocoumarins contained in them. The activity produced by the roots and fruits of Mulkangwhal and *A. purpuraefolia,* however, are not considered to be related to those furanocoumarins which were indentified and demonstrated to have activity in the previous experiment,[4] even though some of many unidentified TLC spots detected in these plant parts might be responsible for manifestation of activity.

Pyranocoumarins such as decursin or decursinol were identified in the various parts of *Angelica* plants in the present experiment (Table II).

No measurable activity of these coumarins could be seen in the previous experiment in which they were tested at a dose of as low as that of furanocoumarins which exerted significant activity[4]. At a higher dose (100mg/kg, i. p.), decursin and decursinol exhibited a significant prolongation of barbiturate-induced hypnosis (data not shown).

Therefore, these results indicate that there may be other constituents in the active plant parts to play roles in giving alteration of barbiturate-induced hypnosis. This phenomenon could be observed obviously in the roots of *A. gigas* which, even though the main constituents of which were pyranocoumarins, exerted very strong activity.[1]

Further studies on coumarin contents and their activities in individual *Angelica* plants should be pursued to elucidate more precise structure-activity relationships of natural coumarins.

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