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CHEMICAL COMPOSITION AND ANTIMICROBIAL ACTIVITY OF ESSENTIAL OILS FROM *Angelica sinensis* (Oliv.) Diels CULTIVATED IN HUNG YEN PROVINCE OF VIETNAM

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ABSTRACT

Essential oils from roots, flowers, fruits, and leaves plus stems of *Angelica sinensis* cultivated in Vietnam were obtained by hydrodistillation and were analyzed using GC/MS-FID. In total, 36, 30, 33, and 27 compounds were found accounting for 98.7%, 98.8%, 99.2%, and 100% of the oils compositions, respectively. (*Z*)-Ligustilide (49.4%, 29.6%, 25.8%, 28.9%) and γ-terpinene (20.6%, 38.5%, 35.5%, 44.2%) were the main components of the respective essential oils. Especially, dictyopterene C (10.8%) was found to be one of the main components of fruit oil. Among the *A. sinensis* essential oil samples tested, the fruit oil revealed the strongest antimicrobial activity against bacteria *Escherichia coli* and yeast *Candida albicans* with median inhibitory concentration values of 0.97 and 0.15 mg/mL, respectively.

Keywords: *Angelica sinensis*, essential oil composition, antimicrobial activity.

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INTRODUCTION

Angelica sinensis (Oliv.) Diels, named "Duong quy" in Vietnamese, belongs to the genus of *Angelica* L., family of Apiaceae Lindl. This plant species contains essential oils with characteristic odor in all of its parts (Vo, 2012). The root of *A. sinensis* is a well-known traditional medicine in Vietnam and other countries (Do et al., 2004; Ministry of Health, 2009; Vo, 2012). Due to its health benefits, it is frequently found not only in medicinal prescriptions but also in various functional foods, dietary supplements, and nutraceuticals around the world. For many years, *A. sinensis* has been widely cultivated for commercial purposes, especially in China and some provinces of Vietnam. Due to its popularity, there have been a substantial number of scientific studies on the plant in general, and on its essential oils, in particular. Chemical studies on *A. sinensis* oils focused on the composition of essential oils obtained from its roots (Tabanca et al., 2008; Wedge et al., 2008; Champakaew et al., 2015) and its leaves and flowers (Nguyen Xuan Dung et al., 1996). Other studies on *A. sinensis* root oils focused on their biological activities, such as anxiolytic activity (Chen et al., 2004), antifungal activity (Tabanca et al., 2008), antioxidant activity (Li et al., 2007), mosquitoes repellent activity (Wedge et al., 2008; Champakaew et al., 2015), antibacterial activity (Mullen et al., 2014), and anti-inflammatory activity (Yao et al., 2015; Li et al., 2016). In Vietnam, there was a report in 1996 on the chemical composition of the essential oils from the leaves and flowers of two cultivars of *A. sinensis*. Unfortunately, at that time, the authors were not able to investigate the root oil of these plants (Nguyen Xuan Dung et al., 1996). In the present study, we report on the chemical composition and antimicrobial activity of essential oils obtained from the roots, flowers, fruits, and a mixture of leaves and stems of *A. sinensis* cultivated in Hung Yen province, Vietnam.

MATERIALS AND METHODS

Plant material

The seeds of a Chinese cultivar of *A. sinensis* were purchased from Duc Thang Ltd Company and grown in Khoai Chau district, Hung Yen province, Vietnam. Fresh materials were collected in May 2020 after 8 months of cultivation and separated into 4 parts: (1) roots (mixture of rhizomes and roots), (2) flowers, (3) fruits (unripe fruits containing seeds), and (4) mixture of leaves and stems. A voucher specimen (HY2001) was deposited at the Herbarium of the Institute of Ecology and Biological Resources, VAST, Vietnam.

Hydro distillation of essential oil

From 1.0 to 1.7 kg of each fresh sample was shredded and hydrodistilled for 4 hours using a Clevenger type apparatus. The essential oils were separated and stored at -5 ^oC until analysis. The oil yields were calculated based on the dry weight of samples determined using A&D Weighing AD-4714A General purpose moisture determination balance.

GC/MS-FID analysis

GC/MS analyses were carried out using an Agilent GC7890A system with Mass Selective Detector (Agilent 5975C). An HP-5MS fused silica capillary column (60 m × 0.25 mm i.d. × 0.25 µm film thickness) was used. Helium was the carrier gas with a flow rate of 1.0 mL/min. The inlet temperature was 250 ^oC and the oven temperature program was as follows: 60 ^oC to 240 ^oC at 4 ^oC/min. The split ratio was 100:1 and the injection volume was 1 µL. The MS analysis was carried out at interface temperature 270 ^oC, MS mode, E.I. detector voltage 1258 V, and mass range 35–450 Da at 4.0 scan/s. FID analysis was carried out using the same chromatographic conditions. The FID temperature was 270 ^oC. Essential oil constituents were identified by their relative retention indices, determined by co-injection of a homologous series of n-alkanes (C5–C30), as well as by comparison of their mass spectral fragmentation patterns with those stored on the MS library NIST08, Wiley09, HPCH1607 (Adams, 2001; Linstrom & Mallard, 2020). Data processing software was MassFinder 4.0 (König et al., 2019). Component relative concentrations were calculated based on the area peak of FID chromatography without standardization.

Screening of antimicrobial activity

The antimicrobial activity of the essential oils was evaluated using 3 strains of Gram-positive test bacteria including *Staphylococcus aureus* (ATCC 13709), *Bacillus subtilis* (ATCC 6633) and *Lactobacillus fermentum* (VTCC N4), 3 strains of Gram-negative test bacteria including *Escherichia coli* (ATCC 25922), *Salmonella enterica* (VTCC) and *Pseudomonas aeruginosa* (ATCC 15442), and 1 yeast *Candida albicans* (ATCC 10231). The ATCC strains were obtained from American Type Culture Collection; the VTCC strains were obtained from Vietnam Type Culture Collection, Institute of Microbiology and Biotechnology, Vietnam National University, Ha Noi. Minimum inhibitory concentration (MIC) and Median inhibitory concentration (IC_{50}) values were measured by the microdilution broth susceptibility assay (Hadacek & Greger, 2000; Cos et al., 2006). Stock solutions of the oil were prepared in dimethylsulfoxide (DMSO). Dilution series were prepared from 1000 µg/mL to 3.9 µg/mL - four steps of four-fold dilution (1000, 250, 62.5, 15.625 and 3.90625 µg/mL) in sterile distilled water in micro-test tubes, from where they were transferred to 96-well microtiter plates. Bacteria grown in double-strength Mueller-Hinton broth or double-strength tryptic soy broth, and fungi grown in double-strength Sabouraud dextrose broth were standardized to 5×10^5 and 1×10^3 CFU/mL, respectively. The last row, containing only the serial dilutions of the sample without microorganisms, was used as a negative control. Sterile distilled water and medium served as a positive control. After incubation at 37 °C for 24 hours, the MIC values were determined at well with the lowest concentration of agents that completely inhibit the growth of microorganisms. The IC_{50} values were determined by the percentage of microorganisms inhibited growth based on the turbidity measurement data of EPOCH2C spectrophotometer (BioTeK Instruments, Inc Highland Park Winooski, USA) and Raw data computer software (Belgium) according to the following equations:

$$\%\ \text{inhibition} = \frac{OD_{control(+)} - OD_{test\ agent}}{OD_{control(+)} - OD_{control(-)}} \times 100\%$$

$$IC_{50} = High_{Conc} - \frac{(High_{Inh\%} - 50\%) \times (High_{Conc} - Low_{Conc})}{(High_{Inh\%} - Low_{Inh\%})}$$

Where: OD: Optical density; control (+): Only cells in medium without antimicrobial agent; test agent: coresponds to a known concentration of antimicrobial agent; control (-): Culture medium without cells. $High_{Conc}/Low_{Conc}$: Concentration of test agent at high concentration/low concentration; $High_{Inh\%}/Low_{Inh\%}$: % inhibition at high concentration/% inhibition at low concentration.

Reference materials: Ampicillin for Gram-positive bacterial strains with MIC values in the range of 0.004 to 1.2 µg/mL, Cefotaxime for Gram-negative bacterial strains with MIC values in the range of 0.07–19.23 µg/mL, Nystatine for the fungal strain with MIC value of 2.8 µg/mL.

RESULTS AND DISCUSSION

Chemical composition of the essential oils

The essential oils obtained from the roots, flowers, fruits, and a mixture of leaves and stems of *A. sinensis* were pale yellow liquids having a lower density than water. Oil yields of 0.10 %, 0.73%, 0.70%, and 0.43% (v/w), calculated on a dry weight basis, were obtained, respectively.

The chemical compositions of the oils are summarized in Table 1. A total of 36, 30, 33, and 27 compounds were found in the respective samples, representing 98.7%, 98.8%, 99.2%, and 100% of the essential oil compositions.

Table 1. Compositions of the essential oils from different parts of *Angelica sinensis*

No.	RI	Components	Compositions (%) of the essential oils			
			Roots	Flowers	Fruits	Leaves & stems
1	930	α-Thujene	-	0.3	0.3	0.3
2	939	α-Pinene	0.2	0.9	0.7	0.9
3	955	Camphene	0.3	1.1	0.8	0.9
4	978	Sabinene	0.2	0.7	0.7	0.5
5	984	β-Pinene	-	0.3	0.2	0.2
6	992	Myrcene	1.7	8.5	4.8	6.9
7	1003	*n*-Octanal	0.3	-	-	-
8	1021	α-Terpinene	-	0.4	0.3	0.4
9	1029	*o*-Cymene	6.1	1.9	3.1	2.0
10	1034	Limonene	0.6	1.9	1.3	1.7
11	1035	β-Phellandrene	0.2	1.2	0.7	1.0
12	1038	(*Z*)-β-Ocimene	2.9	1.1	0.8	3.0
13	1049	(*E*)-β-Ocimene	0.2	-	-	0.1
14	1064	γ-Terpinene	20.6	38.5	35.5	44.2
15	1094	Terpinolene	-	0.1	0.1	0.1
16	1101	Linalool	0.7	0.3	0.2	0.2
17	1162	*n*-Pentylbenzene	0.4	-	-	-
18	1164	Dictyopterene C	1.0	4.6	10.8	2.5
19	1176	(*E*,*E*)-1,3,5-Undecatriene	-	-	0.1	-
20	1185	Terpinen-4-ol	0.3	0.2	0.2	0.2
21	1197	α-Terpineol	0.2	-	-	-
22	1290	Lavandulyl acetate	-	0.2	0.1	-
23	1294	Bornyl acetate	-	-	0.1	-
24	1297	Safrole	0.4	-	-	-
25	1320	*vinyl*-Guaiacol	0.2	-	-	-
26	1409	*n*-Decyl acetate	-	-	0.6	-
27	1437	(*E*)-β-Caryophyllene	0.9	2.9	2.1	2.8
28	1460	(*Z*)-β-Farnesene	0.3	0.3	-	0.5
29	1471	α-Humulene	0.3	0.4	0.2	0.2
30	1474	γ-Decalactone	0.3	-	0.3	-
31	1497	α-Zingiberene	0.2	1.1	0.7	0.5
32	1499	Germacrene D	-	0.6	0.4	0.3
33	1512	(*E*,*E*)-α-Farnesene	-	0.2	-	-
34	1548	Kessane	-	0.3	0.3	-
35	1569	(*E*)-Nerolidol	0.1	0.2	-	-
36	1601	10-*epi*-Junenol	0.5	0.2	0.1	-
37	1604	Caryophyllene oxide	0.3	-	-	0.2
38	1609	Dodecyl acetate	0.6	0.8	6.2	0.3
39	1617	Carotol	0.5	-	-	-

40	1668	Butylphthalide	0.1	-	-	-
41	1678	*n*-Tetradecanol	2.1	-	-	-
42	1690	(*Z*)-3-Butylidenephthalide	4.0	0.5	0.5	0.6
43	1739	Senkyunolide	-	-	0.2	-
44	1740	(*E*)-3-Butylidenephthalide	0.2	-	-	-
45	1760	(*Z*)-Ligustilide	49.4	29.6	25.8	28.9
46	1808	Tetradecyl acetate	0.4	-	0.5	-
47	1820	(*E*)-Ligustilide	1.3	0.6	0.5	0.6
48	1881	*n*-Hexadecanol	0.7	-	-	-
Total			98.7	98.8	99.2	100
Monoterpene hydrocarbons			33.0	55.8	49.3	62.2
Oxygenated monoterpene			1.9	0.5	0.7	0.4
Sesquiterpene hydrocarbons			1.7	5.5	3.4	4.3
Oxygenated sesquiterpene			1.4	0.7	0.4	0.2
Phthalides			55.0	30.7	27.0	30.1

Note: RI = Retention indices.

The number of monoterpene hydrocarbon compounds found in the root, flower, fruit, and mixed leaf and stem essential oils were 10, 13, 13, and 14, accounting for 33.0%, 55.8%, 49.3%, and 62.2% of the total oil composition, respectively. Phthalides include 5, 3, 4, 3 compounds, representing 55.0%, 30.7%, 27.0%, 30.1% of the respective oils. Oxygenated monoterpenes, sesquiterpene hydrocarbons and oxygenated sesquiterpenes were present only in small amounts in all samples (Table 1).

The main constituents of the root oil were (*Z*)-ligustilide (49.4%) and γ-terpinene (20.6%). Other more abundant components were: *o*-cymene (6.9%), (*Z*)-β-ocimene (2.9%), and (*Z*)-3-butylidenphthalide (4.0%). In the flower oil, γ-terpinene (38.5%) and (*Z*)-ligustilide (29.6%) were the main constituents, followed by myrcene (8.5%), dictyopterene C (4.6%), and (*E*)-β-caryophyllene (2.9%). The fruit oil was apparently different from the other oils by the presence of a substantial amount of dictyopterene C (10.8%). Its other main constituents were (*Z*)-ligustilide (25.8%). In addition, myrcene (4.8%), *o*-cymene (3.1%), and dodecyl acetate (6.2%) were identified. The leaf and stem oil had a pattern of the main constituents similar to that of the flower oil with γ-terpinene (44.2%) and (*Z*)-ligustilide (28.9%) being the main constituents, followed by myrcene (6.9%), (*Z*)-β-ocimene (3.0%), and (*E*)-β-caryophyllene (2.8%) (Table 1).

From a total of 48 identified compounds, 19 were found in all 4 oil samples. However, the concentrations of these compounds were different. The most valuable compound of the *A. sinensis* essential oils is (*Z*)-ligustilide - a monomeric phthalide - that was determined in root essential oil at the highest concentration (49.4%), followed by flower oil (29.6%), leaf and stem oil (28.9%), and fruit oil (25.8%). (*Z*)-ligustilide was reported to significantly decrease the areas of infarction and ischemic brain swelling, improve neurological behavioral deficiencies that occur after middle cerebral artery occlusion (Peng et al., 2007), prevent chronic cognitive deficiency and brain damage, thus having therapeutic potential in the treatment of vascular dementia and cerebrovascular failure (Kuang et al., 2008). It was also reported to have anti-inflammatory, anti-cancer, neuroprotective and anti-toxic effects (Chao & Lin, 2011), as well as significantly attenuate PC12 cell death caused by glutamate at concentrations lower than 50 μM (Liu et al., 2017).

Data on the composition of essential oils from *A. sinensis* roots were abundant.

Tabanca et al. (2008) showed that, out of 27 identified compounds, the amount of (*Z*)-ligustilide in an *A. sinensis* root oil from China accounted for 43.1% of the total essential oil concentration, almost equal to the content of this compound in the present study (49.4%). Other main compounds found in that oil were: (*E*)-3-butylidene phthalide (14.5%), (*Z*)-β-ocimene (12.9%), and apiole (11.2%). In another study, the contents of (*Z*)-ligustilide in *A. sinensis* root oils from China and from a Ginseng Enterprise in America were 60.9%−69.2%, while the next high content compounds were: (*E*)-3-butylidene phthalide (5.7−9.8%), (*Z*)-β-ocimene (0.8−16.7%), and (*Z*)-3-butylidene phthalide (1.5%−2.3%) (Wedge et al., 2008; Wedge et al., 2009). Research by Champakaew et al. (2015) showed distinctly different main constituents in *A. sinensis* root oil from Thailand with 50.7% 3-n-butylphthalide and 25.8% (*Z*)-3-butylidenephthalide.

Nguyen Xuan Dung et al. (1996) studied the flowers and leaves oils from two *A. sinensis* varieties cultivated in Vietnam, one from Japan and one from North Korea. The important data therefrom in comparison with our data on the Chinese varieties are shown in Table 2.

As for the leaves oils, the (*Z*)-ligustilide content of the Chinese varieties is significantly higher than those of the Japanese and North Korean varieties, while the γ-terpinene content is accordingly lower (Table 2). The compounds myrcene (6.9%), (*E*)-β-caryophyllene (2.8%) and dictyopterene C (2.5%) were found only in the oil of the Chinese varieties. The compound *p*-cymene (6.5% and 1.2%) was found only in the oils of the Japanese and North Korean varieties.

As for the flower oils, the percentages of the main constituents (*Z*)-ligustilide and γ-terpinene of the Chinese varieties were more similar to those of the Japanese than the North Korean one. On the other hand, the flower oil of the Chinese varieties is characterized by the presence of myrcene (8.5%), dictyopterene C (4.6%) and (*E*)-β-caryophyllene (2.9%), which were not found in the other oils. Dictyopterene C belongs to a group of chemical compounds that are naturally present in marine and freshwater environments. They are sexual attractants, or pheromones, found in several species of brown algae belonging to class Phaeophyceae.

Table 2. Comparison of major compositions of the *Angelica sinensis* essential oils

No.	Components	Compositions (%)					
		Flower oil			Leaf oil		
		Jp[1]	Kr[1]	Ch[2]	Jp[1]	Kr[1]	LS-Ch[2]
1	Myrcene	-	-	8.5	-	-	6.9
2	*p*-Cymene	-	-	-	6.5	1.2	-
3	Limonene	3.3	6.2	1.9	3.8	3.2	1.7
4	(*Z*)-β-Ocimene	1.7	4.0	-	3.2	3.2	0.1
5	γ-Terpinene	44.3	62.3	38.5	59.2	68.3	44.2
6	Dictyopterene C	-	-	4.6	-	-	2.5
7	Linalool	2.2	2.3	0.3	-	-	0.2
8	(*E*)-β-Caryophyllene	-	-	2.9	-	-	2.8
9	(*Z*)-Ligustilide	33.6	13.6	29.6	11.9	6.4	28.9

Note: [1]Nguyen Xuan Dung et al. (1996); [2]Chinese varieties in the present study; LS = leaf and stem; Jp = Japanese varieties; Kr = North Korean varieties.

The composition of essential oils from parts of *A. sinensis* in the present study is in general similar to the ones of *A. sinensis* cultivated in Vietnam (Nguyen Xuan Dung et al., 1996) or purchased from China (Wedge et al., 2008; Wedge et al., 2009) in the previous reports. However, in the present study, essential oils from all 4 parts of *A. sinensis* contain dictyopretene C that has never been identified in the *A. sinensis* essential oils in previous researches. To the best of our knowledge, this is the first report on the chemical composition of essential oil from fruits of *A. sinensis*. It is also the first report on the chemical composition of essential oil from the roots of *A. sinensis* cultivated in Vietnam.

Antimicrobial activity of *Angelica sinensis* essential oils

The antimicrobial activity of the *A. sinensis* essential oils was assessed by the microdilution broth susceptibility assay by determining the MIC and IC_{50} values using 7 strains of microorganisms. The results obtained after 16−24 hours of incubation are presented in Table 3. In the range of test concentrations, only the root oil exhibited antimicrobial activity, with IC_{50} values of 0.97 and 0.15 mg/mL for *E. coli* and *C. albicans*, respectively. All other IC_{50} and MIC values were higher than 1.0 mg/mL.

There were only a few reports on the antimicrobial activity of essential oils from *A. sinensis*. A root oil from Chinese *A. sinensis* containing (*Z*)-ligustilide (43.1%) was tested for antifungal activity against three species of genus *Colletotrichum* using direct-bioautography assay at a concentration of 20 mg/mL in 4 and 8 µL samples placed onto a silica TLC plate. The oil showed moderate activity but appeared to be non-selective. (*Z*)-ligustilide and apiole (11.2%) were shown to be the active components of the oil (Tabanca et al., 2008). The antibacterial activity of an extract of *A. sinensis* roots with canola oil was tested against 3 mastitis-causing pathogens: *Staphylococcus aureus*, *S. chromogenes* and *Streptococcus uberis*. The result showed that treatments at a concentration of 4% (v/v) reduced the growth of *S. chromogenes* as compared with the control, but the effect was much lower than that of thyme oil (Mullen et al., 2014).

Table 3. IC_{50} and MIC values of the essential oils from different parts of *Angelica sinensis*

Microorganisms	Values (mg/mL)	Roots	Flowers	Fruits	Leaves & stems
Staphylococcus aureus	IC_{50}	> 1.0	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0
Bacillus subtilis	IC_{50}	> 1.0	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0
Lactobacillus fermentum	IC_{50}	> 1.0	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0
Salmonella enterica	IC_{50}	> 1.0	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0
Escherichia coli	IC_{50}	0.97 ± 0.02	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0
Pseudomonas aeruginosa	IC_{50}	> 1.0	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0
Candida albicans	IC_{50}	0.15 ± 0.01	> 1.0	> 1.0	> 1.0
	MIC	> 1.0	> 1.0	> 1.0	> 1.0

CONCLUSIONS

The yields of essential oil obtained from *A. sinensis* roots, flowers, fruits, and a mixture of leaves and stems were 0.10%, 0.73%, 0.70%, and 0.43% (v/w) calculated on a dry weight basis, respectively. The number of compounds identified in the respective oils was 36, 30, 33, and 27, accounting for 98.7%, 98.8%, 99.2%, and 100% of the oils compositions. (*Z*)-ligustilide (25.8–49.4%) and γ-terpinene (20.6–44.2%) were the main constituents of all 4 oils. The content of the most desirable component (*Z*)-ligustilide was the highest in the root oil (49.4%), which is comparable to its content in Chinese samples (43.1% and higher). The microdilution broth susceptibility assay for 7 strains of test microorganisms showed that *A. sinensis* root essential oil exhibited antimicrobial activity, with IC_{50} values of 0.97 and 0.15 mg/mL for *E. coli* and *C. albicans*, respectively.

This is the first time that essential oils from all parts of *A. sinensis*, including its fruits, have been investigated. It is also the first time that dictyopterene C was found in an *A. sinensis* essential oil. With the high yields (0.43–0.73% v/w) of essential oils from the aerial parts of *A. sinensis*, much higher than that of the root (0.10%), these parts could be a good source for exploitation and utilization.

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