Exp Appl Acarol (2018) 74:403–414
https://doi.org/10.1007/s10493-018-0249-8

Acaricidal and repellent effects of *Cnidium officinale*-derived material against *Dermanyssus gallinae* (Acari: Dermanyssidae)

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Received: 19 February 2018 / Accepted: 17 March 2018 / Published online: 22 March 2018

Abstract The acaricidal activity of a methanolic extract and fractions from the rhizome of *Cnidium officinale* against *Dermanyssus gallinae* adults was investigated. The *C. officinale* methanolic extract exhibited 100% acaricidal activity after 48 h of treatment at a dose of 4000 ppm. The acaricidal constituents of the plant were sequentially partitioned with several solvents and then purified using silica gel column chromatography and high-performance liquid chromatography. Gas chromatography–mass spectrometry and nuclear magnetic resonance spectroscopy revealed (*Z*)-ligustilide as a constituent of *C. officinale*. Acaricidal activity was examined in three experimental tests (spray, fumigation and contact), with the spraying method being the most effective. The methanolic extract of *C. officinale* showed both contact and fumigant activities, though only fumigant activity was observed with (*Z*)-ligustilide. The fumigant effects of the methanolic extract and (*Z*)-ligustilide caused 86.5 and 62.6% mortality, respectively, of *D. gallinae* adults at 48 h. Among (*Z*)-ligustilide, acaricides (bifenthrin, cypermethrin and spinosad) and butylidenephthalide, bifenthrin displayed the highest acaricidal activity, and the activity of butylidenephthalide was 2.3-fold higher than that of (*Z*)-ligustilide. These results suggest that *C. officinale*-derived material can be used for the development of a control agent for *D. gallinae*.

Keywords *Dermanyssus gallinae* · *Cnidium officinale* · Acaricidal activity · (*Z*)-ligustilide

Hyun Kyung Kim and Seung Ju Lee have contributed equally to this work.

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Introduction

The poultry red mite, *Dermanyssus gallinae* (De Geer), is a blood-sucking ectoparasite that feeds on poultry and occurs worldwide (Axtell and Arends 1990). Moreover, as it transmits various diseases and pathogens, such as Newcastle disease virus, pullorum disease, fowl spirochetosis, and fowl plague, poultry farms suffer considerable loss due to *D. gallinae* (Lancaster and Meisch 1986; Axtell and Arends 1990; Durden et al. 1993; Moro et al. 2009). *Dermanyssus gallinae* causes food intake reduction and decreased immunity in chickens and even death in severe cases (Freeman 1976). Hematophagous during nymph and adult stages, the short life cycle of *D. gallinae* leads to environmental outbreaks (Chauve 1998). In addition, the short period of blood-sucking activity, which is limited to the night, and the high potential of the mites to hide in the gaps of poultry cages, complicate control measures. Therefore, the possibility of disease spread increases because of the likelihood of contacting other hosts (Axtell and Arends 1990; Chauve 1998; Nordenfors et al. 1999).

Dermanyssus gallinae exhibits resistance worldwide to various acaricides; indeed such resistance has been reported on poultry farms in Japan (organophosphates, pyrethroids, and carbamates), Sweden (permethrin), UK (malathion, bendiocarb, cypermethrin, and permethrin) and Korea (amitraz, milbemectin, clothianidin, thiamethoxam, and fenitrothion) (Nordenfors et al. 2001: Fiddes et al. 2005; Murano et al. 2015; Lee et al. 2017). Acaricidal residue tests of chickens in Italy detected carbaryl, a prohibited pesticide, on 37 of 45 poultry farms and permethrin, an unregistered acaricide, on one poultry farm (Marangi et al. 2012). These findings indicate that the indiscriminate use of pesticides on poultry farms is a potential risk to humans and can be associated with environmental pollution. Therefore, the development of safe acaricides is required. Active substances in plants are one such alternative to chemicals (Pitasawat et al. 2007).

Secondary metabolites of plants act as toxic substances, repellents, attractants and growth regulators, and these compounds have been investigated in many studies (Kwon and Ahn 2003; Kim et al. 2004, 2016; Ahn et al. 2006; Park et al. 2012). For example the acaricidal activity of *Asarum sieboldii* var. *seoulense*, *A. heterotropoides*, *Cinnamomum camphora*, *Eugenia caryophyllata* and *Mentha arvensis* var. *piperascens* against *D. gallinae* has been studied, and the acaricidal and repellent activities of various essential oils have also been reported (Kim et al. 2004, 2007, 2016; Nechita et al. 2015). One study on the acaricidal effect of *Cnidium officinale* against *Tyrophagus putrescentiae* indicated that the constituent butylidenephthalide applied as a fumigant has the highest acaricidal potential (Kwon and Ahn 2003).

Cnidium officinale Makino (Apiaceae) is used as a medicinal plant in east Asian countries, and the main constituents are cnidilide, ligustilide, neocnidilide, senkyunolide, butylphthalide, and butylidenephthalide (Bohrmann et al. 1967; Kobayashi et al. 1984; Shin and Park 1994). Ligustilide compounds demonstrate repellent, larvicidal and insecticidal activities against *Anopheles stephensi* and *Sitophilus zeamais* (Wedge et al. 2009; Chu et al. 2011; Osanloo et al. 2017). Moreover, butylidenephthalide compounds have broad insecticidal and acaricidal activities against several insects and acarids, such as *Sitophilus zeamais*, *Drosophila melanogaster*, *Ctenocephalides felis*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* and *Tyrophagus putrescentiae* (Chu et al. 2011; Tsukamoto et al. 2005, 2006; Kwon and Ahn 2003).

The present study aims to investigate the acaricidal and repellent activities of a methanolic extract and fractions of *C. officinale* and to compare them with (*Z*)-ligustilide and

butylidenephthalide, as major constituents of *C. officinale*, as well as three commercial acaricides: bifenthrin, cypermethrin and spinosad.

Materials and methods

Mites

Poultry red mites were supplied from Biogenoci (Suwon, Korea). *Dermanyssus gallinae* was identified by polymerase chain reaction (PCR) according to the method of Potenza et al. (2009). Briefly, *D. gallinae* DNA was extracted using a DNeasy Blood and Tissue kit (Qiagen, Hilden, Germany). The first PCR involved an initial denaturation at 95 °C for 10 min, followed by 35 cycles of 95 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s and a final extension at 72 °C for 10 min. The second PCR involved an initial denaturation at 95 °C for 10 min, followed by 35 cycles of 95 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s and a final extension at 72 °C for 10 min. The primers and amplified product lengths were as follows (5′–3′): ITS1 (530 bp) forward (F)-TCCGTAGGTGAACCTGCGG, reverse (R)-AGAGGAAGTAAAAGTCGTAACA; ITS2 (152 bp) forward (F)-GCGTGTCTA TGCTGCATTTG, reverse (R)-GGGGTCGTCACACTTGATTT. The PCR products were examined on 1.5% agarose gels, with a DNA ladder (100 bp plus DNA; Biofact, Daejeon, Korea) included.

Chemicals

Butylidenephthalide (95% purity) was purchased from Alfa Aesar (Tewksbury, MA, USA). The acaricides used in this study were of commercial grade: bifenthrin 8% WG, cypermethrin 5% EC, and spinosad 10% WG. All acaricides were purchased at a commercial farm supply store.

Isolation and identification

Dried *C. officinale* rhizomes (600 g) were purchased from a medicinal herb shop at Kyoungdong market (Seoul, Korea). The material was powdered and extracted with 3 L methanol at room temperature for 2 days; the extraction was performed 4×. The filtrate was concentrated using a rotary vacuum evaporator (Laborota 4000 Efficient; Heidolph, Schwabach, Germany) to yield 99.6 g of extract. The *C. officinale* rhizome extract was sequentially partitioned into hexane, chloroform, ethyl acetate and water fractions (Fig. 1). The hexane fraction was subjected to column chromatography using a silica gel (Merck 70–230 mesh, 500 g, 6×70 cm) and eluted with a gradient of hexane and ethyl acetate. Column fractions were pooled using preparative thin-layer chromatography (TLC) with a silica gel plate (SILC/UV254, 0.25 mm; Merck, Darmstadt, Germany). The active constituent was purified using an Allure® Silica column (5 µm, 250×4.6 mm; Restek, Bellefonte, PA, USA) and a high-performance liquid chromatography (HPLC) system (Agilent Technologies 1200, Germany). The absorption wavelength was measured by UV spectrophotometry (DU-730; Beckman Coulter, Brea, CA, USA). Molecular weights were assessed via gas chromatography–mass spectrometry (GC–MS, Agilent Technologies 7890A/5975C) and a Hybrid LC/Q-TOF system (Bruker, maXis 4G, Germany). For nuclear magnetic resonance (NMR) spectroscopy, ^{1}H-NMR and ^{13}C-NMR spectra (Bruker, Avance III 400 MHz)

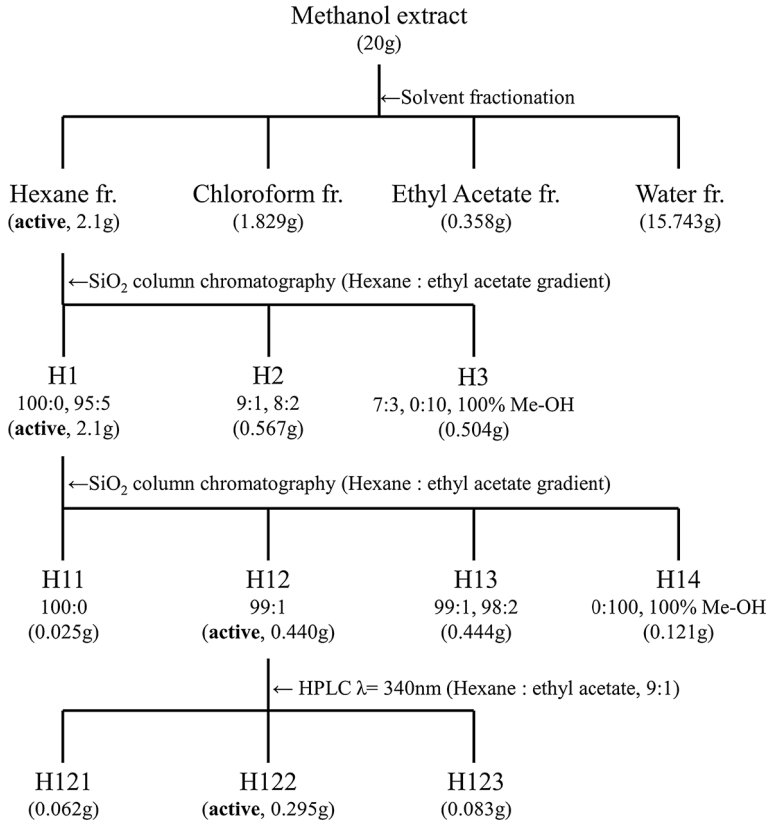

Fig. 1 Isolation procedures for acaricidal constituents from *Cnidium officinale*

provided information on the hydrogen and carbon skeleton, and the structure of the final active compound was identified.

Toxicity bioassay

A spray bioassay combining a hand pump sprayer with a 15-ml falcon tube (Thermo Fisher Scientific, Waltham, MA, USA), was used to evaluate the acaricidal activity of the methanolic extract and fractions of *C. officinale* as well as butylidenephthalide, bifenthrin, cypermethrin and spinosad against adult *D. gallinae*. 15–30 mites were placed in a Petri dish (5.5 × 1.5 cm) with filter paper (5.5 cm diameter). 4–6 concentrations of each test material in 1 ml of solution (100 µl acetone consisting of 1000 ppm Triton-X 100 dissolved in 900 µl distilled water) were sprayed directly onto the mites, after which the dishes were tightly sealed. The treatment and control mites were maintained at 25 ± 1 °C and 70–75% RH in darkness.

Fumigation and contact assays were performed to compare the acaricidal activity of the *C. officinale* extract and (*Z*)-ligustilide. The fumigation assay was similar to the spray assay described above, but contact was prevented between the treated filter paper and the mites. Briefly, 15–30 mites were placed in a Petri dish that was topped with a lid that had a center

hole covered by mesh (200 mesh, 1.5 cm diameter). Filter paper was treated with the test material in 50 µl acetone and then placed on top of the mesh; a solid lid sealed the dish. To maintain humidity, 100 µl distilled water was added to the filter paper.

A contact bioassay was performed to evaluate the toxicity of the *C. officinale* methanolic extract and (*Z*)-ligustilide to mites. Test materials in 50 µl acetone were applied to filter paper (5.5 cm). After drying in a fume hood for 3 min, each treated filter paper was placed into a Petri dish (5.5 cm) with 15–30 mites, and 50 µl distilled water was added to maintain humidity. The dose for each treatment method was the LC_{90} value of the spray assay, with a different dose for each material.

Both male and female adult mites not bloodfed were used in all experiments. Mite mortality was measured by touching the individual with a brush; they were considered to be dead if there was no leg movement at 24 and 48 h after treatment. Control mites were treated with acetone alone. The experiment was repeated 3×. Data from all bioassays were corrected for control mortality using Abbott's formula (Abbott 1925).

Repellent bioassay

The repellent activity of the *C. officinale* methanolic extract and (*Z*)-ligustilide were investigated using a T-tube olfactometer, as described by Yoon et al. (2011). Briefly, for the modified T-tube olfactometer (stem: 4.5 cm; arms: 12 cm at 180°; internal width: 1.5 cm), pressurized air was filtered through activated charcoal, a molecular sieve and silica gel blue before flowing into each arm at 5 L/min. The experiments were conducted as paired choices in which samples were always tested versus acetone only; clean air was used as the control. Repellent activity was determined as the choice by a mite of moving more than 8 cm versus no choice after 30 min of exposure to the filter paper treated with 10 µl of the material diluted with acetone at a ratio of 9:1. For these experiments, mites were maintained at 25 ± 1 °C and 50–60% RH in darkness. All the treatments were replicated 3×.

The selection rate (Sr) of mites was calculated as: (the number of responsive mites in each arm/total number of tested mites) × 100%. The response rate (Rr) was calculated as: [(number of tested mites − number of no responsive mites)/total number of tested mites] × 100%.

Data analysis

The acaricidal activity of the *C. officinale*-derived materials against *D. gallinae* adults was compared and analyzed using Tukey's range test (SAS Instituent 2008). Lethal concentrations (LC_{50} and LC_{90}) of the *C. officinale*-derived materials, the similar compound and the commercial acaricides were calculated using probit analysis (SAS Instituent 2008). Relative toxicity (RT) was calculated as the ratios of the LC_{50} and LC_{90} values of each chemical to the LC_{50} and LC_{90} values of the *C. officinale* methanolic extract. Differences in the response of *D. gallinae* between the treatments and controls in the T-tube olfactometer were analyzed via *t* tests (SAS Instituent 2008).

Results

Isolation of the active constituent

The methanolic extract of *C. officinale* was fractionated to identify acaricidal constituents (Fig. 1). The acaricidal activity of the *C. officinale* extract and fractions using the spray bioassay is reported in Table 1. Significant differences in acaricidal activity were observed among the extract fractions. The hexane fraction at 2000 ppm resulted in 93% *D. gallinae* mortality at 48 h after treatment; mortality of 93.2% was observed for the first subfraction of the hexane fraction (the H1 fraction). The H1 fraction was divided into 4 fractions by open column chromatography, with 100% of the acaricidal activity appearing in the H12 fraction. Fraction H122 caused 80.6% mortality at 400 ppm at 48 h; therefore, this fraction (H122) of *C. officinale* was considered to contain the active constituent.

Spectroscopic analysis

Spectroscopic analysis, including MS and NMR, identified the lactone (*Z*)-ligustilide as the active constituent (H122), and it was isolated as a yellowish oil (Table 2). GC–MS analysis revealed a molecular ion at *m/z* 190 [M]+, and $_{13}$C-NMR spectra revealed 12 carbons in the molecule consisting of four methylenes, one methyl and three non-protonated carbons, as indicated by distortionless enhancement by polarization transfer (DEPT), suggesting the molecular formula $C_{12}H_{14}O_2$ (Fig. 2).

Table 1 Mean (±SE) acaricidal activity (% mortality) of *Cnidium officinale* rhizome derived fractions against *Dermanyssus gallinae* in a spray assay

Isolation step	Concentration (ppm)	Fraction	*n*	Mortality (%)	
				24 h	48 h
1	4000	Methanol extract	68	97.1 ± 2.9	100 ± 0.0
2	2000	Hexane	74	89.8 ± 7.1 a	93.0 ± 4.1 a
		Chloroform	74	73.3 ± 9.3 ab	78.8 ± 9.0 ab
		Ethyl acetate	74	48.9 ± 4.8 b	59.2 ± 8.6 b
		Water	71	5.4 ± 2.8 c	10.2 ± 2.1 c
3	1000	H1	81	93.2 ± 3.8 a	93.2 ± 3.8 a
		H2	77	42.5 ± 3.7 b	52.2 ± 9.8 b
		H3	76	8.8 ± 4.6 c	22.0 ± 5.7 c
4	600	H11	65	3.2 ± 1.6 b	3.2 ± 1.6 b
		H12	69	100.0 ± 0.0 a	100.0 ± 0.0 a
		H13	73	1.4 ± 1.4 b	1.4 ± 1.4 b
		H14	70	0.0 ± 0.0 b	0.0 ± 0.0 b
5	400	H121	78	7.8 ± 0.5 b	18.3 ± 3.5 b
		H122	62	72.1 ± 4.7 a	80.6 ± 0.6 a
		H123	64	0.0 ± 0.0 b	1.7 ± 1.7 c
		Control	69	0.0 ± 0.0	0.0 ± 0.0

Means within an isolation step followed by the same letter are not significantly different (Tukey's test: $P < 0.05$)

Table 2 ^{1}H-NMR and ^{13}C-NMR spectral data for acaricidal components derived from *Cnidium officinale*

No.	Partial structure	δ_C (ppm)	δ_H (ppm)
1	C	169.7	–
2	C	148.6	–
3	C	147.1	–
4	CH_2	18.6	2.58 m
5	CH_2	22.4	2.45 m (2H)
6	CH	129.9	5.99 dt (J=4.0, 9.8 Hz, 1H)
7	CH	117.1	6.26 dt (J=2.0, 9.8 Hz, 1H)
8	C	124.0	–
9	CH	113.0	5.21 t (J=7.6 Hz, 1H)
10	CH_2	28.1	2.35 q (J=7.6 Hz, 2H)
11	CH_2	22.4	1.48 sext (J=7.4 Hz, 2H)
12	CH_3	13.8	0.94 t (J=7.4 Hz, 3H)

The data are consistent with previously reported data (Beck and Stermitz 1995)

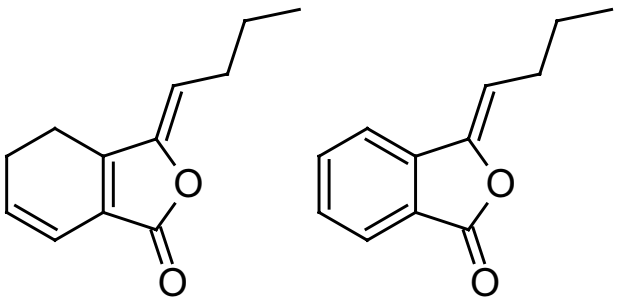

Fig. 2 Structures of (Z)-ligustilide (left) and butylidenephthalide (right)

Acaricidal activity

The acaricidal activity of the methanolic extract of the *C. officinale* rhizome, (*Z*)-ligustilide, butylidenephthalide, and three commercial acaricides was evaluated against poultry red mites in a spray bioassay (Table 3). Bifenthrin showed the highest acaricidal activity, with an RT_{50} value that was 22.2-fold higher than that of the methanolic extract. The acaricidal activity of the *C. officinale* rhizome-derived constituent (*Z*)-ligustilide was 2.8-fold higher than that of the methanolic extract, and that of the similar compound butylidenephthalide was 6.7-fold higher. Although the RT_{50} values of cypermethrin and spinosad were not significantly different from that of the *C. officinale* extract, comparison of the RT_{90} values showed that the activity of spinosad was 4.8-fold higher than that of the methanolic extract.

To investigate the nature or mode of action of the active constituent and the methanolic extract of *C. officinale*, the acaricidal effect was evaluated in spray, contact and fumigation bioassays (Fig. 3). The treatment dose for each method was 101.1 µg/ml of the *C. officinale* methanolic extract and 14.9 µg/ml of (*Z*)-ligustilide.

Table 3 Toxicity of the test compounds against *Dermanyssus gallinae* adults in a spray assay over 48 h of exposure

Compound	*n*	LC_{50} (ppm) (95% CL)	LC_{90} (ppm) (95% CL)	Slope ± SE	x^2	RT_{50}	RT_{90}
Me-OH fraction	260	513.36 (382.87–644.60)	3618 (2661–5640)	1.51 ± 0.171	77.92	1	1
(*Z*)-ligustilide	267	182.79 (153.06–208.40)	532.06 (449.71–682.86)	2.76 ± 0.335	68.08	2.8	6.8
Butylidenephthalide	260	76.68 (70.44–82.87)	160.85 (140.61–195.41)	3.98 ± 0.424	88.20	6.7	22.5
Bifenthrin	194	23.05 (19.87–26.49)	85.00 (67.51–117.34)	2.27 ± 0.223	102.51	22.3	42.6
Cypermethrin	370	398.28 (276.53–557.38)	1389 (889.94–3641)	2.36 ± 0.315	56.3	1.3	2.6
Spinosad	392	329.50 (301.42–357.52)	755.94 (663.19–901.83)	3.55 ± 0.319	124.2	1.6	4.8

CL confidence limits, *RT* relative toxicity

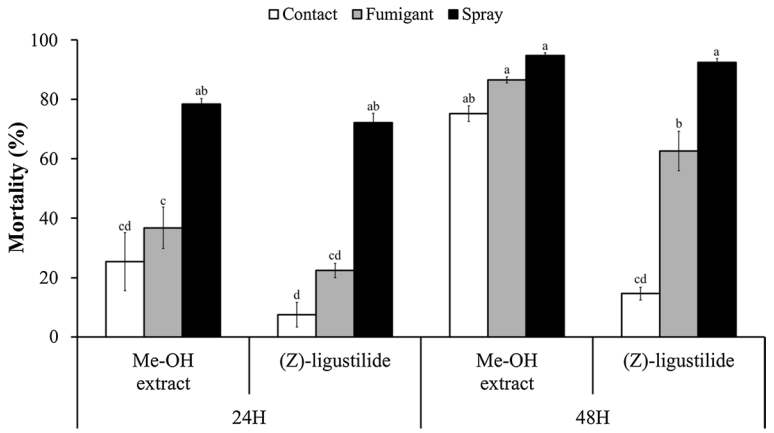

Fig. 3 Mortality of poultry red mite in three bioassays (contact, fumigant and spray) comparing the methanol extract and (*Z*)-ligustilide after 24 and 48 h of treatment

The acaricidal activity of the methanolic extract was greater than 70% in all three bioassays at 48 h, whereas the acaricidal activity of (*Z*)-ligustilide was 14.7, 62.6 and 92.4% in contact, fumigation and spray assays, respectively, at 48 h. The highest mortality for both materials was obtained in spray assays.

Repellent activity

The repellent activity of the methanolic extract of *C. officinale* and (*Z*)-ligustilide were also investigated (Fig. 4). For (*Z*)-ligustilide, the rate of repellent response to treatment was 100%. Although the repellent response rate for the *C. officinale* extract was 91.3%, 25 mites showed no response to either arm.

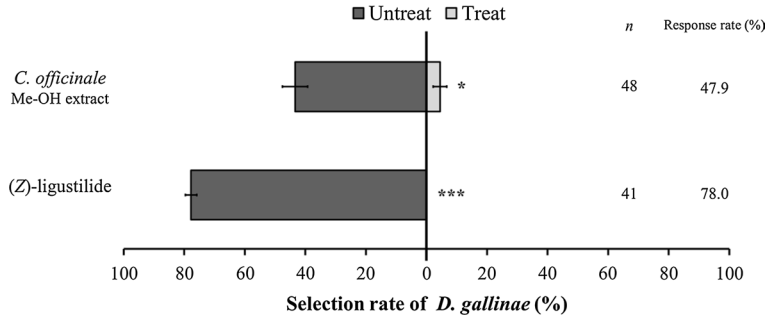

Fig. 4 Selection rate of *Dermanyssus gallinae* adults in a T-tube olfactometer. n = number of tested mites. *$0.001 < P < 0.01$; ***$P < 0.0001$

Discussion

This study investigated the acaricidal activity of *C. officinale*-derived materials against the poultry red mite (*D. gallinae*), which is a problem on poultry farms. Although various *C. officinale* rhizome extracts have exhibited toxic effects on insects, studies on effects against poultry red mite have not been conducted to date (Wedge et al. 2009; Chu et al. 2011; Osanloo et al. 2017; Tsukamoto et al. 2005, 2006; Kwon and Ahn 2003).

In this study, the constituent of *C. officinale* that demonstrated toxicity against mites was identified as (*Z*)-ligustilide. In fact, (*Z*)-ligustilide is the primary compound of various Apiaceae plants, such as *Angelica sinensis*, *A. tenuissima* and *Levisticum officinale*, and it presents anti-inflammatory, antifungal and insecticidal properties (Raal et al. 2008; Chung et al. 2012; Osanloo et al. 2017). Both (*Z*)-ligustilide and butylidenephthalide showed acaricidal activity against *D. gallinae* adults, though butylidenephthalide presented higher activity than (*Z*)-ligustilide. The toxicity of (*Z*)-ligustilide and butylidenephthalide toward *Bemisia tabaci* B bio-type was comparable at 268.4 and 254.2 ppm, respectively; however, the latter was 2.3-fold more toxic than the former against the *B. tabaci* Q bio-type (Chae et al. 2011). Among the three commercial acaricides tested, bifenthrin had the highest toxicity toward poultry red mites. Nonetheless, as resistance to synthesized acaricides can develop over time, continuous pesticide use should be avoided (Lee et al. 2017). Therefore, an alternative treatment to pesticides should be applied to inhibit the development of resistance, and the use of a natural product with a different mechanism of action may be effective (Campos et al. 1995).

The acaricidal activity of (*Z*)-ligustilide and the *C. officinale* methanolic extract was affected by the treatment method, with both materials showing the highest activity in spray bioassays and low activity in contact bioassays. Although (*Z*)-ligustilide exhibited higher activity than the *C. officinale* methanolic extract, the use of the methanolic extract, which showed similar activity in all treatment methods, may be effected for controlling poultry red mites. Similar results were obtained with the essential oil of *Kelussia odoratissima* and (*Z*)-ligustilide against *An. stephensi*, with the *K. odoratissima* essential oil showing 1.8-fold higher insecticidal activity even at 64.24% (*Z*)-ligustilide (Osanloo et al. 2017). This finding can be explained by the synergistic action of various substances in the crude oil (Hummelbrunner and Isman 2001; Miresmailli et al. 2006). However, the LC_{50} value for *An. stephensi* was 80 ppm when using treatment with *Trachyspermum ammi* containing

65% tymol, whereas toxicity increased sharply at 0.48 ppm when using treatment with tymol alone (Pandey et al. 2009). Thus, the substances present in crude extracts can exhibit synergic effects as well as suppressive activity.

Butylidenephthalide derived from *C. officinale* was reported to show higher acaricidal activity in a fumigant assay (100%) than in a contact assay (17%) against the stored-product mite *T. putrescentiae* (Kwon and Ahn 2003). The two compounds were used in a topical application against *S. zeamais* adults, and insecticidal activity (LD_{50}) was observed at 10.23 µg/adult for (*Z*)-ligustilide and at 15.81 µg/adult for butylidenephthalide (Chu et al. 2011).

In our study, the acaricidal activity observed in contact and fumigation bioassays using the *C. officinale* extract increased with time. However, significant differences were not observed over time in the spraying assay. Overall, the highest activity was observed in the spray assay because the solvent added during spraying may affect the cuticle layer and increase permeability of the material (Armstrong et al. 1951).

In our repellency experiment, (*Z*)-ligustilide exhibited higher activity than the *C. officinale* extract. However, using a *C. officinale* extract that is equally active against mites in various treatment methods is more effective for use in the field. Crude *C. officinale* extracts have the benefits of a low economic cost and resistance development avoidance because they are not subjected to a purification process (Osanloo et al. 2017).

Based on the results presented here, (*Z*)-ligustilide is effective for the control of poultry red mite, though spraying crude *C. officinale* extract is considered to be effective because it presents contact and fumigation effects. Therefore, (*Z*)-ligustilide and the *C. officinale* extract may be useful as acaricidal agents in the control of *D. gallinae* adult populations.

Acknowledgements This project was support by Ministry of Trade, Industry and Energy (Project No. R0005538), Republic of Korea.

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