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Acaricidal Toxicity of 2′-Hydroxy-4′-methylacetophenone Isolated from *Angelicae koreana* Roots and Structure−Activity Relationships of Its Derivatives

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ABSTRACT: The acaricidal activities of 2′-hydroxy-4′-methylacetophenone derived from *Angelica koreana* roots and its derivatives against *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, and *Tyrophagus putrescentiae* were examined by vapor phase and contact toxicity bioassays. In the vapor phase toxicity bioassay, 2′-methylacetophenone (1.25 $\mu g/cm^2$) was 8.0 times more toxic against *D. farinae* than benzyl benzoate (10.00 $\mu g/cm^2$), followed by 3′-methylacetophenone (1.26 $\mu g/cm^2$), 4′-methylacetophenone (1.29 $\mu g/cm^2$), 2′-hydroxy-4′-methylacetophenone (1.75 $\mu g/cm^2$), and 2′-hydroxy-5′-methylacetophenone (1.96 $\mu g/cm^2$). In the contact toxicity bioassay, 3′-methylacetophenone (0.58 $\mu g/cm^2$) was 17.24 times more effective against *D. farinae* than benzyl benzoate (7.52 $\mu g/cm^2$), followed by 2′-methylacetophenone (0.64 $\mu g/cm^2$), 2′-hydroxy-4′-methylacetophenone (0.76 $\mu g/cm^2$), 4′-methylacetophenone (0.77 $\mu g/cm^2$), and 2′-hydroxy-5′-methylacetophenone (1.16 $\mu g/cm^2$). The acaricidal activities of 2′-hydroxy-4′-methylacetophenone derivatives against *D. pteronyssinus* and *T. putrescentiae* were similar to those against *D. farinae*. In terms of structure−activity relationships, acaricidal activity against the three mite species changed with the introduction of hydroxyl and methyl functional groups onto the acetophenone skeleton. Furthermore, some of 2′-hydroxy-4′-methylacetophenone derivatives could be useful for natural acaricides against three mite species.

KEYWORDS: *acaricidal activity, Angelica koreana, Dermatophagoides spp., structure−activity relationships, Tyrophagus putrescentiae*

INTRODUCTION

House dust contains contactants such as fungal spores, insects, and mites.[1] Among these contactants, the American house dust mite, *Dermatophagoides farinae* (Hughes), and the European house dust mite, *Dermatophagoides pteronyssinus* (Trouessart), are known as major sources of potent allergens that cause asthma, atopic dermatitis, and perennial rhinitis.[2,3] The stored food mite, *Tyrophagus putrescentiae* (Schrank), was recognized as an etiologic factor among bakers, farmers, and workers consistently handling infested food products.[4,5] These three mite species are also recognized as the dominant species among a wide variety of mites within Korean households: *D. farinae* (65.3% of the total), *D. pteronyssinus* (20.6%), and *T. putrescentiae* (6.5%).[1] These mites are controlled through improved hygiene standards, reduction of humidity levels, and the use of synthetic acaricides such as benzyl benzoate and *N*,*N*-diethyl-*m*-toluamide (DEET).[6,7] Despite the availability and use of synthetic acaricides, their repeated use has caused the development of resistance in mites and adverse effects in nontarget organisms.[8] These problems highlight the need for selective acaricides.[9]

Recent studies have focused on active compounds derived from plants as mite control products[10] because they biodegrade to nontoxic products, have low potential to cause resistance, and have target-selective activation.[11,12] *Angelica koreana* (Maximowicz), a member of the Umbelliferae family, is commonly used as a traditional Korean medicine for the treatment of arthropathy, inflammation, and pyrexia.[13−15] *A. koreana* contains compounds such as coumarin derivatives (bergapten, imperetorin, isoimperetorin, kaholinin, oxypeucedanin, oxypeucedanin-hydrate, prangolarin, and xanthotoxol), monoterpene derivatives (camphene, δ-3-carene, *p*-cymene, limonene, α-phellandrene, α-pinene, and β-pinene), and sesquiterpene derivatives (angelikoreanone, *m*-cresol, eudesmol, and osthol).[15] Previous studies have reported that phytochemicals derived from *Angelica* spp. can be used as antibacterial, anti-inflammatory, antithrombotic, antiulcer, antihepatotoxic, and melanogenesis-inhibiting agents.[14] However, acaricidal and insecticidal activities of *A. koreana* have not been reported in the literature until now. This aim of this study was to evaluate the acaricidal activities of the essential oil and active constituents isolated from *A. koreana*. Furthermore, structure−activity relationships with respect to acaricidal activity and molecular functionalization were also explored.

MATERIALS AND METHODS

Chemicals. Benzyl benzoate, 2′,4′-dihydroxyacetophenone, 2′,6′-dihydroxyacetophenone, 2′-hydroxy-4′-methylacetophenone, 2′-hydroxy-5′-methylacetophenone, 4′-hydroxy-2′-methylacetophenone, 2′-methylacetophenone, 3′-methylacetophenone, and 4′-methylacetophenone were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals were of reagent grade.

Sample Preparation. The air-dried roots (2 kg) of *A. koreana* were purchased from a local market in Jeonju, Korea, and identified by Prof. Sang-Hyun Lee at the Department of Forestry, Chonbuk National University, and Republic of Korea. Samples were ground in a blender and extracted using a steam-distillation extraction technique. The water was removed on anhydrous sodium sulfate, and the

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extracted oil was concentrated by rotary evaporation (EYELA model Auto Jack NAJ-100, Japan) at room temperature. The essential oil was stored in a refrigerator at 4 °C to keep volatile compounds from evaporating.[16]

Isolation and Identification. The essential oil of *A. koreana* roots (15 g) was isolated by silica gel column chromatography (Merck 70−230 mesh, 600 g, 550 mm i.d. × 700 mm; Rahway, NJ, USA) and successively eluted with hexane:ethyl acetate (10:0 to 0:10, v/v). Each fraction was loaded on a thin layer chromatography (TLC) plate in order to identify similar fraction patterns. Ultimately five fractions were obtained and referred to as AK-1 through AK-5. The acaricidal activity of each of the five fractions was evaluated against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* at a concentration of 80 $\mu g/cm^2$. AK-2 had potent acaricidal activity against *Dermatophagoides* spp. and *T. putrescentiae*. Therefore, rechromatography of active AK-2 (3.2 g) was conducted on a silica gel column using hexane:ethyl acetate (4:1, v/v) and four fractions (AK-21 to AK-24) were obtained. Among these fractions, AK-23 had potent acaricidal activity against the three mite species. Prep HPLC (Japan Analytical Industry Co., Ltd., Tokyo, Japan) was used to departmentalize AK-23. AK-23 (1.4 g) was separated into three fractions (AK-231 to AK-233) using a Jaigel GS series column (GS 310 500 mm + GS 310F 300 mm × 2) with chloroform (100%) as the mobile phase at a flow rate of 1 mL/min and UV detection (225 nm). AK-231 (650 mg) had the highest acaricidal activity among these fractions. Next, a Jaigel W series column (W252 500 mm + W253 500 mm) with chloroform (100%) as the mobile phase at a flow rate of 1.5 mL/min was used. Finally, the active component (AK-2312, 270 mg) was isolated. The structure of AK-2312 was determined using nuclear magnetic resonance (NMR) spectroscopy. ^1H and ^{13}C NMR were measured using a JNM-EX600 (Jeol Ltd., Tokyo, Japan) spectrometer in deuterochloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard at 600 and 150 MHz, respectively. Additionally, 1D NMR (DEFT) and 2D NMR ($^1H-^1H$ COSY and HMQC) were used to determine the connection between carbons and protons.

Mites. Stock cultures of *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* had been kept in the laboratory for ten years without external exposure to any known synthetic acaricides. These mites were bred in cages (15 × 12 × 6 cm) containing 30 g of sterilized artificial diet (fry feed No. 1 and dried yeast, 1:1 by weight) at 25 ± 1 °C and 75% relative humidity in darkness. The fry feed (Miropa) was purchased from Korea Special Feed Meal Co. Ltd., Jeonju, South Korea. The feed consisted of crude protein (44.0%), cellulose (4.0%), crude lipid (3.0%), P (2.0%), and Ca (1.8%).

Vapor Phase Toxicity Bioassay. This experiment was performed to evaluate acaricidal activity against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* using a transparent microtube (2 mL, Greiner Bio-One GmbH, Germany). This method was modified from the method described by Jeong et al.[17] Each of the sample concentrations (80, 40, 20, 10, 5, 2.5, 1.25, and 0.63 $\mu g/cm^2$) was dissolved in 20 μL of acetone and then injected on a paper disk (Advantec, 8 mm in diameter, 1 mm thick; Toyo Roshi, Tokyo, Japan). The negative control (acetone) and the positive control (benzyl benzoate) were used at the same volume on the paper disks. These disks were dried under a fume hood for 15 min and then implanted into the lid of a microtube. Also, a piece of thin fabric was inserted into the lid of a microtube in order to prevent contact of mites from applied disk. Twenty adult *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* each were placed in each microtube, which was then sealed with the lid. The treated and control groups were incubated for 24 h at 25 ± 1 °C and 75% relative humidity in darkness. The mortality was determined by observing the number of dead mites under a binocular microscope (20×, Olympus, Tokyo, Japan). Dead mites were verified by their lack of movement when prodded with a pin. All treatments were replicated three times.

Contact Toxicity Bioassay. The acaricidal activities of the active compound isolated from *A. koreana* and its derivatives against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* were evaluated using a filter paper method. The modified bioassay method was described by Jang et al.[18] Briefly, concentrations of the compounds used were 80, 40, 20, 10, 5, 2.5, 1.25, 0.63, and 0.32 $\mu g/cm^2$. 40 μL of the solution was applied to the filter paper (Whatman, 50 mm in diameter, 55 μm thick; GE Healthcare, Little Chalfont, U.K.). The filter paper intended for the control group was treated with acetone alone. After drying in a fume hood for 15 min, each filter paper was transferred to the bottom of a Petri dish (50 mm in diameter × 8 mm deep). Twenty individual adult mites were transferred to each Petri dish, and then the lid was closed. The number of dead mites was determined after 24 h using a binocular microscope, and LD_{50} values were calculated using probit analysis. All treatments were replicated three times.

Statistical Analysis. The percent mortality and 50% lethal dose (LD_{50}) values were determined via probit analysis and then analyzed using analysis of variance (ANOVA) with Scheffe's post hoc tests at the $P < 0.05$ level of significance. Relative toxicity (RT) was calculated as the ratio of commercial acaricide LD_{50}/each test chemical LD_{50}, as described previously.[17,19]

RESULTS AND DISCUSSION

The acaricidal activity of the essential oil derived from *A. koreana* roots against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* was determined by a vapor phase toxicity bioassay and compared with that of synthetic acaricide such as benzyl benzoate (Table 1). Based on the LD_{50} values of *D. farinae*, the essential oil (3.53 $\mu g/cm^2$) was about 2.83 times more toxic than benzyl benzoate (10.0 $\mu g/cm^2$). Against *D. pteronyssinus*, the essential oil (4.15 $\mu g/cm^2$) was 2.31 times more active than benzyl benzoate (9.58 $\mu g/cm^2$). For *T. putrescentiae*, the essential oil (6.27 $\mu g/cm^2$) was approximately 1.95 times more effective than benzyl benzoate (12.23 $\mu g/cm^2$). Mortality of negative control was not observed in the *Dermatophagoides* spp. and *T. putrescentiae*. These results indicate that the target mite species are differentially susceptible to the essential oil of *A. koreana* roots. Such species specificity has been reported in previous studies.[15,18,19]

Table 1. Acaricidal Activities of *A. koreana* Oil and Synthetic Acaricides against Three Mite Species in the Vapor Phase Toxicity Bioassay

sample	mite species	LD_{50} ($\mu g/cm^2$)	95% CL	RT[a] (benzyl benzoate)
A. koreana oil	*D. farinae*	3.53	3.40−4.69	2.83
	D. pteronyssinus	4.15	3.43−5.10	2.31
	T. putrescentiae	6.27	5.59−7.31	1.95
benzyl benzoate	*D. farinae*	10.00	9.32−11.21	1.00
	D. pteronyssinus	9.58	9.18−11.15	1.00
	T. putrescentiae	12.23	11.15−13.24	1.00

[a]Relative toxicity = LD_{50} value of benzyl benzoate/LD_{50} value of each chemical.

To isolate the active component of the *A. koreana* oil, silica gel column chromatography and prep HPLC were performed with single or mixed organic solvents. As a result, AK-2312 was isolated and identified by spectroscopic analyses including EI-MS, ^1H NMR, and ^{13}C NMR. The isolated compound was characterized as 2′-hydroxy-4′-methylacetophenone (Figure 1). 2′-Hydroxy-4′-methylacetophenone ($C_9H_{10}O_2$; MW, 150.17; appearance, liquid; boiling point, 245 °C): EI-MS (70 eV) m/z M^+ 226, 207, 184, 153, 135, 107, 77, 53; ^1H NMR ($CDCl_3$, 600 MHz) δ 12.275 (OH, s), 7.598−7.611 (1H, d), 6.779 (1H, s), 6.701−6.715 (1H, d), 2.594 (3H, s), 2.347 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 204.233, 162.794, 148.413, 130.929, 120.540, 118.712, 117.869, 26.803, 22.275 (Table 2). The spectrometric and spectroscopic findings for 2′-hydroxy-4′-

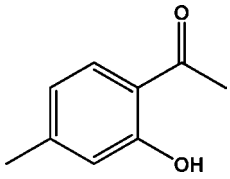


Figure 1. Structure of 2′-hydroxy-4′-methylacetophenone isolated from *A. koreana*.

Table 2. ^{1}H and ^{13}C NMR[a] Assignment for AK-2312

carbon	partial structure	δ_C (ppm)	δ_H (ppm)
1	C	130.9290	
2	COH	162.7938	12.2761 (s[b])
3	CH	118.7115	6.7792 (s)
4	C	148.4125	
5	CH	117.8690	6.7013−6.7151 (d, J = 8.28 Hz)
6	CH	120.5403	7.5982−7.6119 (d, J = 8.22 Hz)
7	C	204.2334	
8	CH_3	26.8033	2.5943 (s)
9	CH_3	22.2745	2.3468 (s)

[a] ^{1}H and ^{13}C spectra were obtained in $CDCl_3$ at 600 and 150 MHz, respectively. [b] s, singlet; d, doublet.

methylacetophenone were consistent with those in a previously reported study.[20]

In the vapor phase toxicity bioassay, the acaricidal activities of 2′-hydroxy-4′-methylacetophenone isolated from the *A. koreana* oil and its derivatives against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* were compared with that of synthetic acaricide (benzyl benzoate) (Table 3). The LD_{50} value against *D. farina* indicated that 2′-methylacetophenone (1.25 $\mu g/cm^2$) was the most active compound, and was about 8.0 times more toxic than benzyl benzoate (10.00 $\mu g/cm^2$), followed by 3′-methylacetophenone (1.26 $\mu g/cm^2$), 4′-methylacetophenone (1.29 $\mu g/cm^2$), 2′-hydroxy-4′-methylacetophenone (1.75 $\mu g/cm^2$), and 2′-hydroxy-5′-methylacetophenone (1.96 $\mu g/cm^2$). Against *D. pteronyssinus*, 4′-methylacetophenone (1.35 $\mu g/cm^2$) was 7.09 times more toxic than benzyl benzoate (9.58 $\mu g/cm^2$), followed by 3′-methylacetophenone (1.36 $\mu g/cm^2$), 2′-methylacetophenone (1.43 $\mu g/cm^2$), 2′-hydroxy-5′-methylacetophenone (2.22 $\mu g/cm^2$), and 2′-hydroxy-4′-methylacetophenone (2.92 $\mu g/cm^2$). For *T. putrescentiae*, 4′-methylacetophenone (1.88 $\mu g/cm^2$) was 6.50 times more effective than benzyl benzoate (12.23 $\mu g/cm^2$), followed by 2′-hydroxy-5′-methylacetophenone (1.95 $\mu g/cm^2$), 3′-methylacetophenone (2.01 $\mu g/cm^2$), 2′-methylacetophenone (2.68 $\mu g/cm^2$), and 2′-hydroxy-4′-methylacetophenone (3.49 $\mu g/cm^2$). However, 2′,4′-dihydroxyacetophenone, 2′,6′-dihydroxyacetophenone, and 4′-hydroxy-2′-methylacetophenone had no activity against *Dermatophagoides* spp. or *T. putrescentiae* in the vapor phase toxicity bioassay.

In the contact toxicity bioassay, 3′-methylacetophenone (0.58 $\mu g/cm^2$) was the most active compound against *D. farinae*, and was about 12.96 times more toxic than benzyl benzoate (7.52 $\mu g/cm^2$), followed by 2′-methylacetophenone (0.64 $\mu g/cm^2$), 2′-hydroxy-4′-methylacetophenone (0.76 $\mu g/cm^2$), 4′-methylacetophenone (0.77 $\mu g/cm^2$), and 2′-hydroxy-5′-methylaceto-

Table 3. Acaricidal Activities of 2′-Hydroxy-4′-methylacetopenone Derivatives and Synthetic Acaricides against Three Mite Species in the Vapor Phase Toxicity Bioassay

chemical	mite species	LD_{50} ($\mu g/cm^2$)	95% CL	RT[a]
2′,4′-dihydroxyacetophenone	*D. farinae*	–[b]	–	–
	D. pteronyssinus	–	–	–
	T. putrescentiae	–	–	–
2′,6′-dihydroxyacetophenone	*D. farinae*	–	–	–
	D. pteronyssinus	–	–	–
	T. putrescentiae	–	–	–
2′-methylacetophenone	*D. farinae*	1.25	1.21−1.58	8.00
	D. pteronyssinus	1.43	1.29−1.86	6.69
	T. putrescentiae	2.68	2.76−3.29	4.56
3′-methylacetophenone	*D. farinae*	1.26	1.15−1.66	7.93
	D. pteronyssinus	1.36	1.27−1.83	7.04
	T. putrescentiae	2.01	2.06−2.47	6.08
4′-methylacetophenone	*D. farinae*	1.29	1.18−1.65	7.75
	D. pteronyssinus	1.35	1.27−1.71	7.09
	T. putrescentiae	1.88	1.59−2.12	6.50
2′-hydroxy-4′-methylacetophenone	*D. farinae*	1.75	1.43−2.05	5.71
	D. pteronyssinus	2.92	2.58−3.35	3.28
	T. putrescentiae	3.49	3.18−3.74	3.50
2′-hydroxy-5′-methylacetophenone	*D. farinae*	1.96	1.74−2.16	5.10
	D. pteronyssinus	2.22	1.92−2.51	4.31
	T. putrescentiae	1.95	1.63−2.28	6.27
4′-hydroxy-2′-methylacetophenone	*D. farinae*	–	–	–
	D. pteronyssinus	–	–	–
	T. putrescentiae	–	–	–
benzyl benzoate	*D. farinae*	10.00	9.32−11.21	1.00
	D. pteronyssinus	9.58	9.18−11.15	1.00
	T. putrescentiae	12.23	11.15−13.24	1.00

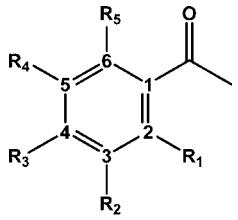
[a] Relative toxicity = LD_{50} value of benzyl benzoate/LD_{50} value of each chemical. [b] No activity.

Table 4. Acaricidal Activities of 2′-Hydroxy-4′-methylacetopenone Derivatives and Synthetic Acaricides against Three Mite Species in the Contact Toxicity Bioassay

chemical	mite species	LD_{50} ($\mu g/cm^2$)	95% CL	RT[a]
2′,4′-dihydroxyacetophenone	*D. farinae*	–[b]	–	–
	D. pteronyssinus	–	–	–
	T. putrescentiae	–	–	–
2′,6′-dihydroxyacetophenone	*D. farinae*	–	–	–
	D. pteronyssinus	–	–	–
	T. putrescentiae	–	–	–
2′-methylacetophenone	*D. farinae*	0.64	0.32–0.97	11.75
	D. pteronyssinus	0.75	0.40–1.10	8.02
	T. putrescentiae	1.45	1.19–1.72	7.31
3′-methylacetophenone	*D. farinae*	0.58	0.23–0.88	12.96
	D. pteronyssinus	0.61	0.36–0.89	9.86
	T. putrescentiae	1.09	0.78–1.36	9.72
4′-methylacetophenone	*D. farinae*	0.77	0.47–1.03	9.76
	D. pteronyssinus	0.85	0.64–1.04	7.08
	T. putrescentiae	1.02	0.26–1.58	10.39
2′-hydroxy-4′-methylacetophenone	*D. farinae*	0.76	0.46–1.02	9.89
	D. pteronyssinus	1.29	0.98–1.53	4.66
	T. putrescentiae	1.36	1.07–1.64	7.79
2′-hydroxy-5′-methylacetophenone	*D. farinae*	1.16	0.91–1.39	6.48
	D. pteronyssinus	1.33	1.05–1.63	4.52
	T. putrescentiae	1.27	0.95–1.57	8.34
4′-hydroxy-2′-methylacetophenone	*D. farinae*	–	–	–
	D. pteronyssinus	–	–	–
	T. putrescentiae	–	–	–
benzyl benzoate	*D. farinae*	7.52	4.21–10.90	1.00
	D. pteronyssinus	6.02	3.69–9.10	1.00
	T. putrescentiae	10.60	8.10–12.72	1.00

[a]Relative toxicity = LD_{50} value of benzyl benzoate/LD_{50} value of each chemical. [b]No activity.

Table 5. Structure–Activity Relationships of 2′-Hydroxy-4′-methylacetophenone Derivatives (Vapor Phase Toxicity Bioassay)



Acetophenone

						LD_{50} ($\mu g/cm^2$)		
compound	R_1	R_2	R_3	R_4	R_5	*D. farinae*	*D. pteronyssinus*	*T. putrescentiae*
2′,4′-dihydroxyacetophenone	OH	H	OH	H	H			
2′,6′-dihydroxyacetophenone	OH	H	H	H	OH			
2′-methylacetophenone	CH_3	H	H	H	H	1.25	1.43	2.68
3′-methylacetophenone	H	CH_3	H	H	H	1.26	1.36	2.01
4′-methylacetophenone	H	H	CH_3	H	H	1.29	1.35	1.88
2′-hydroxy-4′-methylacetophenone	OH	H	CH_3	H	H	1.75	2.92	3.49
2′-hydroxy-5′-methylacetophenone	OH	H	H	CH_3	H	1.96	2.22	1.95
4′-hydroxy-2′-methylacetophenone	CH_3	H	OH	H	H			

phenone (1.16 $\mu g/cm^2$) (Table 4). Against *D. pteronyssinus*, 3′-methylacetophenone (0.61 $\mu g/cm^2$) was 9.86 times more toxic than benzyl benzoate (6.02 $\mu g/cm^2$), followed by 2′-methylacetophenone (0.75 $\mu g/cm^2$), 4′-methylacetophenone (0.85 $\mu g/cm^2$), 2′-hydroxy-4′-methylacetophenone (1.29 $\mu g/cm^2$), and 2′-hydroxy-5′-methylacetophenone (1.33 $\mu g/cm^2$). For *T. putrescentiae*, 4′-methylacetophenone (1.02 $\mu g/cm^2$) was 10.39 times more effective than benzyl benzoate (6.02 $\mu g/cm^2$), followed by 3′-methylacetophenone (1.09 $\mu g/cm^2$), 2′-hydroxy-5′-methylacetophenone (1.27 $\mu g/cm^2$), 2′-hydroxy-4′-methylacetophenone (1.36 $\mu g/cm^2$), and 2′-methylacetophenone (1.45 $\mu g/cm^2$). However, 2′,4′-dihydroxyacetophenone, 2′,6′-dihydroxyacetophenone, and 4′-hydroxy-2′-methylacetophenone had no activity against *Dermatophagoides* spp. or *T. putrescentiae* in the contact toxicity bioassay. These results show that 2′-hydroxy-4′-methylacetophenone derivatives (except for

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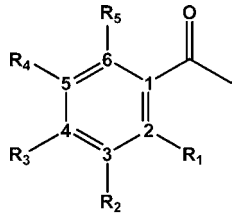
Table 6. Structure−Activity Relationships of 2′-Hydroxy-4′-methylacetophenone Derivatives (Contact Toxicity Bioassay)



Acetophenone

compound	R_1	R_2	R_3	R_4	R_5	LD_{50} ($\mu g/cm^2$)		
						D. farinae	*D. pteronyssinus*	*T. putrescentiae*
2′,4′-dihydroxyacetophenone	OH	H	OH	H	H			
2′,6′-dihydroxyacetophenone	OH	H	H	H	OH			
2′-methylacetophenone	CH_3	H	H	H	H	0.64	0.75	1.45
3′-methylacetophenone	H	CH_3	H	H	H	0.58	0.61	1.09
4′-methylacetophenone	H	H	CH_3	H	H	0.77	0.85	1.02
2′-hydroxy-4′-methylacetophenone	OH	H	CH_3	H	H	0.76	1.29	1.36
2′-hydroxy-5′-methylacetophenone	OH	H	H	CH_3	H	1.16	1.33	1.27
4′-hydroxy-2′-methylacetophenone	CH_3	H	OH	H	H			

2′,4′-dihydroxyacetophenone, 2′,6′-dihydroxyacetophenone, and 4′-hydroxy-2′-methylacetophenone) had potent vapor phase and contact toxicity against *Dermatophagoides* spp. and *T. putrescentiae*.

Tables 5 and 6 show the relative activities of 2′-hydroxy-4′-methylacetophenone derivatives (2′-methylacetophenone, 3′-methylacetophenone, 4′-methylacetophenone, 2′-hydroxy-4′-methylacetophenone, and 2′-hydroxy-5′-methylacetophenone) and synthetic acaricide in the vapor phase and contact toxicity bioassays. In the case of *Dermatophagoides* spp., the contact toxicity of 2′-hydroxy-4′-methylacetophenone derivatives was about 1.59 to 2.33 times more toxic than the vapor phase toxicity. Against *T. putrescentiae*, the contact toxicity of 2′-hydroxy-4′-methylacetophenone derivatives was approximately 1.54 to 9.69 times greater than the vapor phase toxicity. Similarly, Lee et al.[21] reported that the acaricidal activities of piperazine derivatives against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* were more effective in the filter paper method than in the fumigant method. These results indicate that the 2′-hydroxy-4′-methylacetophenone derivatives were more effective in the contact toxicity bioassay than in the vapor phase bioassay.

To evaluate the structure−activity relationships between 2′-hydroxy-4′-methylacetophenone derivatives and acaricidal activities against *Dermatophagoides* spp. and *T. putrescentiae*, LD_{50} values of 2′-hydroxy-4′-methylacetophenone derivatives were compared to those of acetophenone with functional groups (hydroxyl and methyl groups) in various positions (Tables 5 and 6). 2′-Methylacetophenone, 3′-methylacetophenone, and 4′-methylacetophenone containing a methyl group (R_1, R_2, or R_3 position) in the acetophenone skeleton had potent acaricidal activities while 2′,4′- and 2′,6′-dihydroxyacetophenone, which were formed by introducing a hydroxyl group (R_1, R_3, or R_5 position) into the acetophenone skeleton, had no acaricidal activity against the three mite species. 2′-Hydroxy-4′-methylacetophenone and 2′-hydroxy-5′-methylacetophenone, which were generated by adding a methyl group (R_3 or R_4) to 2′-hydroxyacetophenone, exhibited strong acaricidal activity against *Dermatophagoides* spp. and *T. putrescentiae*. In contrast, 4′-hydroxy-2′-methylacetophenone (the addition of a methyl group (R_1) to 4′-hydroxyacetophenone) did not exhibit acaricidal activity against the three mite species. In previous studies, Lee et al.[22] reported that the insecticidal activities of quinoline derivatives (2-hydroxyquinoline, 4-hydroxyquinoline, 6-hydroxyquinoline, 8-hydroxyquinoline, 2-methylquinoline, 4-methylquinoline, 6-methylquinoline, and 8-hydroxy-2-methylquinoline) against *Laodelphax striatellus*, *Nilaparvata lugens*, and *Sogatella furcifera* increased when hydroxyl and methyl groups were added. Furthermore, antifungal activity against wood-rot fungi was influenced by α-methylcinnamic acid, 2-methylcinnamic acid, 3-methylcinnamic acid, and 4-methylcinnamic acid, which are all formed via the addition of methyl groups in different positions on cinnamaldehyde.[23] Taken together, the results of this study and previous studies suggest that changes in acaricidal activity against the three mite species are related to the introduction of functional groups (hydroxyl and methyl groups).

According to Material Safety Data Sheet (MSDS) from Sigma-Aldrich,[24] the oral LD_{50} values of 2′,4′-dihydroxyacetophenone and 4′-methylacetophenone in mice are 2,830 mg/kg and 1,400 mg/kg, respectively. These results indicate that 2′-hydroxy-4′-methylacetophenone derivatives have a relatively low acute toxicity toward mammals. In this regard, the results of this study and those of previous studies indicate that 2′-hydroxy-4′-methylacetophenoe derivatives containing hydroxyl and methyl groups may be helpful in the development of an ecofriendly acaricide for the control of house dust and stored food mites. Further studies should be conducted to evaluate the stability of 2′-hydroxy-4′-methylacetophenone derivatives and their potential toxicity in mammals.

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REFERENCES

(1) Ree, H. I.; Jeon, S. H.; Lee, I. Y.; Hong, C. S.; Lee, D. K. Fauna and geographical distribution of house dust mites in Korea. *Korean J. Parasitol.* **1997**, *35*, 9−17.

(2) Platts-Mills, T. A. E.; Chapman, M. D. Dust mites: immunology, allergic disease, and environmental control. *J. Allergy Clin. Immunol.* **1987**, *80*, 755−775.

(3) Richard, S.; Platts-Mills, T. A. E. Epidemiology of dust-mite-related disease. *Exp. Appl. Acarol.* **1992**, *16*, 141−151.

(4) Van der Heide, S.; Niemeijer, N. R.; Hovenga, H.; de Monchy, J. G. R.; Dubois, A. E. J.; Kauffman, H. F. Prevalence of sensitization to the storage mites *Acarus siro*, *Tyrophagus putrescentiae*, and *Lepidoglyphus destructor* in allergic patients with different degrees of sensitization to the house-dust mite *Dermatophagoides pteronussinus*. *Allergy* **1998**, *53*, 426−430.

(5) Matsumoto, T.; Hisano, T.; Hamaguchi, M.; Miike, T. Systemic anaphylaxis after eating storage-mite-contaminated food. *Int. Arch. Allergy Immunol.* **1996**, *109*, 197−200.

(6) Adilah, N.; Fitzharris, P.; Crane, J.; Siebers, R. W. The effect of frequent vacuum cleaning on the house dust mite allergen. *N. Z. Med. J.* **1997**, *28*, 438−439.

(7) Bischoff, E. R.; Fischer, A.; Liebenberg, B.; Kniest, F. M. Mite control with low temperature washing-II. Elimination of living mites on clothing. *Clin. Exp. Allergy* **1998**, *28*, 60−65.

(8) Pollart, S. M.; Chapman, M. D.; Platts-Mills, T. A. House dust sensitivity and environmental control. *Immunol. Allergy Clin. North Am.* **1987**, *14*, 591−603.

(9) Shin, S. H.; Choi, G. H.; Choi, D. S.; Kwon, O. K.; Im, G. J.; Park, J. U.; Choi, B. R.; Kim, T. W.; Kim, J. H. Insecticidal activity of the crude extract and its fractions of Custard apple (*Annona reticulate* L.). *J. Appl. Biol. Chem.* **2010**, *53*, 21−24.

(10) Park, I. L.; Lee, H. S.; Lee, S. G.; Park, J. D.; Ahn, Y. J. Insecticidal and fumigant activities of *Cinnamomum cassia* bark-derived materials against *Mechoris ursulus* (Coleoptera: Attelabidae). *J. Agric. Food Chem.* **2000**, *48*, 2528−2531.

(11) Isman, M. B. Botanical insecticides, deterrents, and repellents in modern agriculture and an increasingly regulated world. *Annu. Rev. Entomol.* **2006**, *51*, 45−66.

(12) Ahn, Y. J.; Lee, S. B.; Lee, H. S.; Kim, G. H. Insecticidal and acaricidal activity of carvacrol and β-thujaplicine derived from *Thujopsis dolabrata* var. *hondai* sawdust. *J. Chem. Ecol.* **1998**, *24*, 81−90.

(13) Roh, E.; Yun, C. Y.; Lee, J. W.; Lee, C.; Hwang, B. Y.; Oh, S. T.; Jung, S. T.; Han, S. B.; Kim, Y. S. Hypopigmenting activity of bisabolangelone isolated from *Angelica Koreana* Maxim. In α-melanocyte stimulating hormone-activated B16 or melan-a cells. *Planta Med.* **2011**, *77*, 248−251.

(14) Seo, E. K.; Kim, K. H.; Kim, M. K.; Cho, M. H.; Choi, E. W.; Kim, K. N.; Mar, W. C. Inhibitors of 5α-reductase type I in LNCaP cells from the roots of *Angelica koreana*. *Planta Med.* **2002**, *68*, 162−163.

(15) Chi, H. J.; Kim, H. S. Studies on essential oils of plants of Angelica Genus in Korea (IV) −essential oils of *Angelicae Koreanae* Radix. *Korean J. Pharmacogn.* **1993**, *24*, 111−115.

(16) Song, H. Y.; Yang, J. Y.; Suh, J. W.; Lee, H. S. Acaricidal activities of apiol and its derivatives from *Petroselinum sativum* seeds against *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Tyrophagus putrescentiae*. *J. Agric. Food Chem.* **2011**, *59*, 7759−7764.

(17) Jeong, E. Y.; Kim, M. G.; Lee, H. S. Acaricidal activity of triketone analogues derived from *Leptospermum scoparium* oil against house-dust and stored-food mites. *Pest Manage. Sci.* **2008**, *65*, 327−331.

(18) Jang, Y. S.; Lee, C. H.; Kim, M. K.; Kim, J. H.; Lee, S. H.; Lee, H. S. Acaricidal activity of active constituent isolated in *Chamaecyparis obtusa* leaves against *Dermatophagoides* spp. *J. Agric. Food Chem.* **2005**, *53*, 1934−1937.

(19) Lim, J. H.; Kim, H. W.; Jeon, J. H.; Lee, H. S. Acaricidal constituents isolated from *Sinapis alba* L. seeds and structure-activity relationships. *J. Agric. Food Chem.* **2008**, *56*, 9962−9966.

(20) Shin, Y. S.; Lee, O. G.; Park, C. B.; Lee, H. J.; Choi, B. J.; Ham, I.; Choi, H. Y.; Seong, N. S.; Cha, S. W. Two new components from the roots of *Angelicae koreana* Kitagawa. *Chem. Nat. Compd.* **2007**, *43*, 652−654.

(21) Lee, C. H.; Kim, H. W.; Lee, H. S. Acaricidal properties of piperazine and its derivatives against house-dust and stored-food mites. *Pest Manage. Sci.* **2009**, *65*, 704−710.

(22) Lee, C. H.; Jeon, J. H.; Lee, S. G.; Lee, H. S. Insecticidal properties of euphorbiaceae: *Sebastiania corniculata*-derived 8-hydroxyquinoline and its derivatives against three planthopper species (Hemiptera: Delphacidae). *J. Korean Soc. Appl. Biol. Chem.* **2010**, *53*, 464−469.

(23) Cheng, S. S.; Liu, J. Y.; Chang, E. H.; Chang, S. T. Antifungal activity of cinnamaldehyde and eugenol congeners against wood-rot fungi. *Bioresour. Technol.* **2008**, *99*, 5145−5149.

(24) Science Lab Inc. *Material safety data sheet*; Science Lab Inc.: Houston, TX, USA, 2010.