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Toxicity of Bisabolangelone from *Ostericum koreanum* Roots to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (Acari: Pyroglyphidae)

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The acaricidal activity of materials derived from the roots of *Ostericum koreanum* (Apiaceae) toward adults of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* was examined by direct contact and vapor phase toxicity bioassays. Results were compared with those of three acaricides: benzyl benzoate, dibutyl phthalate, and *N*,*N*-diethyl-*m*-toluamide (DEET). The active principle was identified as the sesquiterpenoid bisabolangelone by spectroscopic analysis. In fabric-piece contact toxicity bioassays using adult *D. farinae*, bisabolangelone (1.88 μg/cm^2) was more toxic than benzyl benzoate (11.91 μg/cm^2), DEET (62.20 μg/cm^2), or dibutyl phthalate (79.54 μg/cm^2), based on 24-h LD_{50} values. Against adult *D. pteronyssinus*, bisabolangelone (1.79 μg/cm^2) was similarly more active than benzyl benzoate (9.65 μg/cm^2), DEET (64.45 μg/cm^2), and dibutyl phthalate (77.79 μg/cm^2). In vapor phase toxicity tests with both mite species, bisabolangelone was equitoxic in closed versus open containers. These results indicate that bisabolangelone was largely toxic through contact action. Bisabolangelone merits further study as a potential contact acaricide or lead for the control of house dust mites.

KEYWORDS: ***Ostericum koreanum*; Apiaceae; botanical acaricide; house dust mite; *Dermatophagoides farinae*; *Dermatophagoides pteronyssinus*; contact action; bisabolangelone**

INTRODUCTION

The American house dust mite, *Dermatophagoides farinae* (Hughes), and the European house dust mite, *Dermatophagoides pteronyssinus* (Trouessart), are two of the most important pyroglyphid mites due to their cosmopolitan occurrence and abundance in homes (*1*, *2*). They are a major source of multiple potent allergens (*2*−*4*) and are causally associated with sudden infant death syndrome (*5*). Control of house dust mites has been principally achieved through the use of synthetic chemicals, such as pirimiphos-methyl, benzyl benzoate, dibutyl phthalate, and pyrethroids (*1*, *3*, *6*). Although effective, their repeated use has resulted in resistance (*7*), has undesirable effects on nontarget organisms, and raises human health concerns (*2*, *8*). These problems have highlighted the need for selective control alternatives for house dust mites.

Plants have been suggested as an alternative source for house dust mite control products because some of them are selective, biodegrade to nontoxic products, and have few harmful effects on nontarget organisms and the environment (*9*, *10*). These potential new acaricides can be applied to beds, sofas, furniture, and carpeted floors in the same manner as current acaricides (*2*). In addition, certain plants and their constituents have been proposed as alternatives to the most commonly used acaricide, benzyl benzoate, because they are exempt from toxicity data requirements by the U.S. Environmental Protection Agency (EPA) as minimum risk pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (*11*). Because of this, much effort has been focused on plants and their constituents as potential sources of commercial house dust mite control agents. In a preliminary experiment, a methanolic extract of the roots of *Ostericum koreanum* Kitagawa (Apiaceae, formerly Umbelliferae) showed potent acaricidal activity toward adults of *D. farinae* and *D. pteronyssinus*.

This paper describes a laboratory study aimed at isolating acaricidal constituents from the roots of *O. koreanum* active toward adults of *D. farinae* and *D. pteronyssinus* and determining their acaricidal route of action. The acaricidal activity of *O. koreanum* root-derived compounds was also compared with that of three acaricides: benzyl benzoate, *N*,*N*-diethyl-*m*-toluamide (DEET), and dibutyl phthalate.

MATERIALS AND METHODS

Apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JMN-ECX 400 spectrometer at 400 and 100 MHz (TMS as an internal standard), respectively, and chemical shifts are given in δ (parts per

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million). HMBC, HMQC, and COSY spectra were acquired using the Delta software. UV spectra were obtained in ethanol with a Biomate 5 spectrophotometer, FT-IR spectra on a Nicolet Magna 550 series II, and mass spectra on a JEOL GSX 400 spectrometer. Optical rotation was measured with an Autopol III polarimeter.

Plant Material. The dried roots of *O. koreanum* were purchased from Boeun medicinal herb shop, Gyungdong Market, Seoul, Korea. A voucher specimen (KSW-06) was deposited in the Research Institute for Agriculture and Life Sciences, School of Agricultural Biotechnology, Seoul National University, Seoul, Korea.

Dust Mites. Colonies of *D. farinae* and *D. pteronyssinus* were separately maintained in plastic containers (12.5 × 10.5 × 5.0 cm) containing 25 g of sterilized diet (1 part fry feed no. 1 and 1 part dried yeast, w/w) at 25 ± 1 °C and 70−75% relative humidity (RH) in darkness. The fry feed was purchased from Korea Special Feed Meal Co., Ltd., Incheon, Korea. Dried yeast was supplied by Dae Heung Pharm. Co., Seoul, Korea.

Extraction and Isolation. Air-dried roots (2 kg) of *O. koreanum* were pulverized and extracted two times with 10 L of methanol at room temperature for 2 days and filtered. The combined filtrate was concentrated under vacuum at 40 °C to yield ∼202 g of an extract. The extract (140 g) was sequentially partitioned into hexane (10.6 g), chloroform (29.1 g), ethyl acetate (2.7 g), butanol (36.7 g), and water (55.2 g) portions for subsequent bioassay. The organic solvent portions were concentrated to dryness by rotary evaporation at 40 °C, and the water portion was concentrated at 50 °C. The most active hexane fraction afforded compound **1** (540 mg) by repeated recrystallization in hexane at −20 °C.

Contact Toxicity Bioassay. A fabric-piece contact toxicity bioassay (*12*) was used to evaluate the toxicity of *O. koreanum* root-derived materials and three acaricides, benzyl benzoate, DEET, and dibutyl phthalate, applied to cotton fabric, to adults (7−10 days old) of *D. farinae* and *D. pteronyssinus*. Six concentrations of *O. koreanum* root-derived materials and acaricides in 80 μL of methanol were applied to circular pieces of black cotton fabric (5-cm diameter). Control fabric circles received 80 μL of methanol. After drying in a fume hood for 2 min, each fabric circle was placed on the bottom of a Petri dish (5 × 1 cm). Groups of 26−38 adult mites were individually placed on the fabric, and each Petri dish was covered. Treated and control (methanol only) mites were held at the same conditions used for colony maintenance. Evaluation of adulticidal activity was made at 24 h after treatment under a binocular microscope (20×). Mites were considered to be dead if appendages did not move when they were prodded with a wooden dowel. All treatments were replicated three times.

In separate experiments, poisoning symptoms of 6.1 μg/cm^2 of the compound isolated to adults of *D. farinae* and *D. pteronyssinus* were determined at 15−30-min intervals under a binocular microscope. This concentration of the test compound gave >90% mortality at 24-h post-treatment.

Vapor Phase Toxicity Bioassay. Experiments were conducted to determine whether lethal activity of *O. koreanum* root-derived compound and acaricides toward adults (7−10 days old) of *D. farinae* and *D. pteronyssinus* was attributed to contact or fumigant toxicity (*12*). Briefly, groups of 30−40 adults were placed on the bottom of a Petri dish and covered with a lid that had a fine wire screen (200 mesh; 4-cm diameter) covering a central hole (3-cm diameter). Black cotton fabric circles (5-cm diameter) were treated either with 50.9 μg/cm^2 of the compound isolated or benzyl benzoate or with 152.7 μg/cm^2 of DEET or dibutyl phthalate in 80 μL of methanol. The treated fabric circle was placed on top of the wire screen, which prevented direct contact of mites with either the compound isolated or acaricide. Petri dishes were either sealed with a solid lid (method A) to investigate the potential vapor phase toxicity of the test materials or left unsealed (method B). Treated and control (methanol only) mites were held at the same conditions used for colony maintenance. Mortalities were determined at 24 h after treatment. All treatments were replicated three times.

Data Analysis. Mortality percentages were determined and transformed to arcsine square root values for analysis of variance (ANOVA). The Bonferroni multiple-comparison method was used to test for significant differences among the test materials (*13*). A paired *t* test was used to test for significant differences between two treatment methods (*13*). The LD_{50} values were calculated by probit analysis (*13*). Acaricidal activity was considered to be significantly different when 95% confidence limit levels of the LD_{50} values failed to overlap.

Table 1. Lethal Activity of *O. koreanum* Root-Derived Materials against Adults of *D. farinae* and *D. pteronyssinus* Using the Fabric-Piece Contact Toxicity Bioassay, Exposed for 24 h at 50.9 μg/cm^2

	mortality,[a] % (mean ± SE)			
material	no. of mites	*D. farinae*	no. of mites	*D. pteronyssinus*
methanol extract	94	79 ± 2.3a	98	79 ± 1.8a
hexane fraction	106	92 ± 1.1a	107	91 ± 1.2a
chloroform fraction	109	19 ± 1.2b	107	18 ± 1.4b
ethyl acetate fraction	92	9 ± 2.8b	85	9 ± 3.0b
butanol fraction	100	12 ± 3.3b	100	14 ± 2.6b
water fraction	96	15 ± 2.8b	99	17 ± 1.3b

[a] Means within a column followed by the same letter are not significantly different (P = 0.05, Bonferroni method).

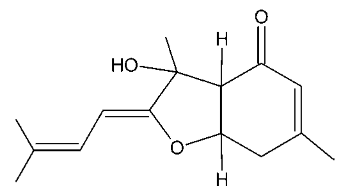

Figure 1. Structure of bisabolangelone.

RESULTS

Bioassay-Guided Fractionation and Isolation of Active Principles. Fractions obtained from the methanolic extract of *O. koreanum* roots were bioassayed by direct contact application (**Table 1**). Significant differences in lethal activity against adults of *D. farinae* and *D. pteronyssinus* in fractions of the extract were observed and used to identify peak activity fractions for the next step in the purification. At a dose of 50.9 μg/cm^2, the hexane fraction exhibited the most pronounced lethal activity at 24 h after treatment, whereas little or no lethal activity was observed with the other four fractions. There was no mortality in the methanol-treated controls.

Fabric-piece contact toxicity bioassay-guided fractionation of the hexane fraction afforded an active principle identified by spectroscopic analysis, including MS and NMR. The active principle was characterized as the bisabolane sesquiterpenoid bisabolangelone (**Figure 1**). This compound was identified on the basis of the following evidence: white or pale yellow needles; $[\alpha]^{20}_D$ +195.2° (c 0.025, MeOH); UV (EtOH) λ_{max} (ϵ) = 247 (33643); IR (KBr, cm^{-1}), υ_{max} = 3342 (−OH), 1640 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.62 (3H, s), 1.72 (3H, s), 1.79 (3H, s), 2.01 (3H, s), 2.65 (1H, d, J = 6.9 Hz), 2.72 (2 H, d, J = 6.0 Hz), 3.37 (1H, s), 4.88 (1H, q, J = 4.5 Hz), 5.37 (1H, d, J = 11.4 Hz), 5.99 (1H, m), 6.02 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 18.2, 24.6, 26.0, 27.3, 34.9, 53.6, 76.1, 78.5, 94.3, 117.7, 127.2, 132.5, 158.1, 160.1, 196.8; EI-MS, m/z (relative intensity) = 248 $[M]^+$ (13), 230 (100), 215 (62), 148 (78), 109 (66); HR EI-MS, $C_{15}H_{20}O_3$ found 248.1405 $[M^+]$, calcd 248.1407.

Acaricidal Activity of Test Compounds. On the basis of 24-h LD_{50} values, bisabolangelone was the most toxic acaricide, followed by benzyl benzoate, DEET, and dibutyl phthalate (**Table 2**). This compound was 6-, 33-, and 42-fold more toxic than benzyl benzoate, DEET, and dibutyl phthalate, respectively. No mortality was observed in the methanol-treated controls.

Table 2. Toxicity of Bisabolangelone and Acaricides to Adult *D. farinae* Using the Fabric-Piece Contact Toxicity Bioassay, Exposed for 24 h

compound	no. of mites	slope ± SE	LD_{50} (μg/cm^2)	95% cl[a]	RT[b]
bisabolangelone	449	4.7 ± 0.39	1.88	1.76–2.01	6.34
benzyl benzoate	411	3.2 ± 0.30	11.91	10.79–13.18	1.00
DEET	488	4.2 ± 0.33	62.20	57.38–66.99	0.19
dibutyl phthalate	419	6.6 ± 0.61	79.54	75.86–83.49	0.15

[a] cl, confidence limit. [b] Relative toxicity = LD_{50} value of benzyl benzoate/LD_{50} value of each chemical.

Table 3. Toxicity of Bisabolangelone and Acaricides to Adult *D. pteronyssinus* Using the Fabric-Piece Contact Toxicity Bioassay, Exposed for 24 h

compound	no. of mites	slope ± SE	LD_{50} (μg/cm^2)	95% cl[a]	RT[b]
bisabolangelone	434	5.5 ± 0.43	1.79	1.68–1.90	5.40
benzyl benzoate	424	3.7 ± 0.31	9.65	8.83–10.51	1.00
DEET	458	4.0 ± 0.51	64.45	59.05–69.18	0.15
dibutyl phthalate	419	6.9 ± 0.63	77.79	74.36–81.47	0.12

[a] cl, confidence limit. [b] Relative toxicity = LD_{50} value of benzyl benzoate/LD_{50} value of each chemical.

Table 4. Lethal Activity of Bisabolangelone and Acaricides toward Adult *D. farinae* Using the Vapor Phase Toxicity Bioassay during a 24-h Exposure

		mortality (%) (±SE)				
compound	dose (μg/cm^2)	no. of mites	A[a]	no. of mites	B[a]	*P* value[b]
bisabolangelone	50.9	109	20 ± 2.4	90	8 ± 0.6	0.032
benzyl benzoate	50.9	105	16 ± 1.2	96	12 ± 1.7	0.923
DEET	152.7	107	16 ± 1.4	103	8 ± 2.0	0.041
dibutyl phthalate	152.7	102	10 ± 2.8	90	8 ± 1.4	0.460

[a] A, vapor in closed containers; B, vapor in open containers. [b] Student *t* test.

The toxicity of bisabolangelone along with standard acaricides benzyl benzoate, DEET, and dibutyl phthalate toward adult *D. pteronyssinus* in the fabric-piece contact toxicity bioassay is recorded in **Table 3**. As judged by 24-h LD_{50} values, bisabolangelone was 5, 36, and 43 times more active than benzyl benzoate, DEET, and dibutyl phthalate, respectively.

Poisoning Symptoms. Typical poisoning symptoms in both mite species from bisabolangelone were examined in the fabric-piece contact toxicity bioassay. This compound caused death without knockdown, but there were no distinguishable symptoms between *D. farinae* and *D. pteronyssinus*. Bisabolangelone resulted in lethargy of treated mites, leading to death.

Acaricidal Route of Action. After 24 h of exposure to 50.9 μg/cm^2, weak lethal activity was observed following the treatment with bisabolangelone in either closed (method A) or open containers (method B), suggesting little or no fumigant action of this compound (**Table 4**). Similar differences in the response of adult *D. farinae* to benzyl benzoate, DEET, and dibutyl phthalate in treatments A and B were likewise observed.

The fumigant toxicity of bisabolangelone and test acaricides to adult *D. pteronyssinus* was also examined (**Table 5**). After 24 h of exposure to 50.9 μg/cm^2, weak lethal activity was produced following the treatment with bisabolangelone in either closed or open containers.

Table 5. Lethal Activity of Bisabolangelone and Acaricides toward Adult *D. pteronyssinus* Using the Vapor Phase Toxicity Bioassay during a 24-h Exposure

		mortality (%) (±SE)				
compound	dose (μg/cm^2)	no. of mites	A[a]	no. of mites	B[a]	*P* value[b]
bisabolangelone	50.9	108	16 ± 2.4	94	10 ± 2.0	0.167
benzyl benzoate	50.9	110	19 ± 1.3	101	10 ± 0.8	0.008
DEET	152.7	104	15 ± 2.4	93	8 ± 2.6	0.120
dibutyl phthalate	152.7	110	12 ± 2.0	100	9 ± 2.2	0.072

[a] A, vapor in closed containers; B, vapor in open containers. [b] Student *t* test.

DISCUSSION

In East Asia, the root of *O. koreanum* has long been considered to have medicinal properties such as an analgesic agent in the treatment of headache, fever, arthritis, and rheumatism (*14*). It contains various compounds such as benzopyranoids [furanocoumarins (imperatorin, isoimperatorin, koreanin, oxypeucedanin, prangolarine) (*15*, *16*), deoxygenated coumarin (aesculin) (*17*), furo-1-benzopyran (cimifugin) (*17*)] and sesquiterpenes (bisabolangelone) (*18*). Very little information exists with respect to managing house dust mites with *O. koreanum* despite its excellent pharmacological actions (*14*). In the present study, *O. koreanum* root-derived materials exhibited potent acaricidal activity toward adults of *D. farinae* and *D. pteronyssinus*.

Various compounds such as alkaloids, phenolics, and terpenoids exist in plants and jointly or independently contribute to bioactivity. The adult *D. farinae* is found to be more tolerant to eugenol, isoeugenol, and methyleugenol than the adult *D. pteronyssinus* (*19*). It has been reported that susceptibility to some plant essential oils such as almond bitter oil, caraway oil, and perilla oil was greater in adult *D. farinae* than in adult *D. pteronyssinus* (*20*, *21*). No significant difference in toxicity of either paeonol and benzoic acid (*22*) or butylidenephthalide (*12*) between *D. farinae* and *D. pteronyssinus* has been noted. In the current study, the acaricidal principle of *O. koreanum* root was identified as bisabolangelone. This is the first report on the acaricidal activity of bisabolangelone. The acaricidal activity of this compound toward adults of *D. farinae* and *D. pteronyssinus* was much more pronounced than that of either benzyl benzoate, DEET, or dibutyl phthalate. Additionally, there was no significant difference in toxicity of bisabolangelone between *D. farinae* and *D. pteronyssinus*. Bisabolangelone is found to possess antifeedant activity against adults and larvae of three coleopteran stored-product insects (*23*) and larvae of *Leptinotarsa decemlineata* (Say) (*23*, *24*), *Pieris brassicae* (L.) (*25*), and *Peridroma saucia* (Hübner) (*26*).

Investigation of poisoning symptoms and mode of action of acaricidal natural products and acaricides is of practical importance for dust mite control because it may give useful information on the most appropriate formulation and delivery means. Five types of poisoning symptoms of chemicals against mites have been reported: a knockdown-type death caused by *N. sericea* leaf oil in *D. farinae* and *D. pteronyssinus* (*27*); death following uncoordinated behavior but without knockdown by (*E*)-cinnamaldehyde, cinnamyl alcohol, salicylaldehyde, benzyl benzoate, and DEET in both dust mites (*28*); death associated with lethargy by butylidenephthalide (*12*) and isoeugenol and methyleugenol (*21*) in both dust mites; death associated with desiccation by several monoterpenes such as fenchone, linalool, menthone, and pulegone in *Tyrophagus putrescentiae* (Schrank) (*29*); and death related with a characteristic depression of the dorsal surface of the idiosoma by tricalcium phosphate and ferric phosphate in *T. putrescentiae* (*30*). Fumigant activity of plant compounds, such as alkanes, alcohols, aldehydes, and terpenoids, particularly monoterpenoids, against adults of *D. farinae* and *D. pteronyssinus* has been reported for butylidenephthalide (*12*), paeonol (*22*), and eugenol, isoeugenol, and methyleugenol (*21*). In the present study, bisabolangelone caused death without knockdown. Additionally, there was little difference in lethal activity of bisabolangelone in closed versus open containers against adults of *D. farinae* and *D. pteronyssinus*. These results indicate that the mode of delivery of bisabolangelone was likely by contact action, although the exact mode of action of this compound remains to be proven.

The results of this study indicate that bisabolangelone could be useful as a contact acaricide for *D. farinae* and *D. pteronyssinus*. For the practical use of this compound as a novel acaricide to proceed, further research is necessary on safety issues of bisabolangelone on human health. Other areas requiring attention are acaricidal mode of action and formulations to improve the acaricidal potency and stability and to reduce cost.

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