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Acaricidal properties of 5-methylfurfural identified from *Valeriana fauriei* and its structural analogues against synanthropic mites and Asian longhorned tick with color alterations

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Abstract

Acaricidal activities and color alterations of 5-methylfurfural derived from *Valeriana fauriei* essential oil and its structural analogues against *Dermatophagoides farinae*, *D. pteronyssinus*, *Haemaphysalis longicornis* and *Tyrophagus putrescentiae* were evaluated in the present study. Based on the LD_{50} values of 5-methylfurfural and its analogues, 4,5-dimethylfurfural showed the highest acaricidal activity (LD_{50}; 9.95, 9.91, and 7.12 μg/cm^2), followed by 5-methylfurfural (11.87, 11.00, and 8.59 μg/cm^2), furfural (12.94, 13.25, and 10.36 μg/cm^2), and *V. fauriei* essential oil (15.15, 13.64, and 10.14 μg/cm^2) against *D. farinae*, *D. pteronyssinus* and *T. putrescentiae*, respectively. However, all tested compounds did not show the acaricidal activities against *H. longicornis*. Interestingly, the color alterations of the mites and ticks were observed by furfural, 5-methylfurfural, and 4,5-dimethylfurfural from colorless to red brown during the acaricidal experiments. Furthermore, 4,5-dimethylfurfural which exhibited the highest acaricidal activity was formulated as nanoemulsion. The nanoemulsion of 4,5-dimethylfurfural showed higher acaricidal activity than it was emulsified in ethanol. The nanoemulsion was also found to show color changes of the mites and ticks from colorless to red brown. The results suggest that 5-methylfurfural and its analogues could be developed as an effective and easy-to-recognize acaricides to mites and ticks.

Keywords: Acaricidal activity, 5-methylfurfural, Mite color alteration, *Dermatophagoides* spp., *Tyrophagus putrescentiae*

Introduction

Global warming has influenced human health in many ways by accelerating the spread of various infectious agents. Especially, climate change has caused the growth of the arthropods to act as the allergens or pathogen vectors that occur the serious human health problems. The house dust mites, *Dermatophagoides farinae* and *D. ptronyssinus* (Acari: Pyroglyphidae) have been known to be the major source of potent allergens in house, which contribute to a number of allergic diseases such as asthma, eczema, and allergic rhinitis [1]. The storage mite, *Tyrophagus putresceantiae* (Acari: Acaridae) is found in stored products and induces allergic diseases with workers engaged in agriculture and food industries [2]. Furthermore, storage mite often spreads toxic bacteria and fungi such as *Aspergillus* spp. and *Penicillium* spp., because they can survive and grow by feeding on some seed-borne fungi [3]. The Asian longhorned tick, *Haemaphysalis longicornis* is an obligate blood-sucking ectoparasite and feed on a wide variety of vertebrate hosts [4], and is well known

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to carry the severe fever with thrombocytopenia syndrome (SFTS), including fever, gastrointestinal symptoms, thrombocytopenia, and leukocytopenia [5, 6]. In these reasons, the arthropods have been the cause of decreasing the quality of human life and health.

One of the conventional control methods against mites and ticks is use of synthetic acaricides, such as avermectin, benzyl benzoate, chloropyrifos-methyl, DEET, etc. Although the synthetic acaricides are effective for the control of mites and ticks, long-term and excessive uses of synthetic acaricides can lead to adverse effects, such as resistance to acaricides, poor sustainability of the chemicals, environmental contamination, and side effects in non-target organisms [7]. Therefore, development of more efficient and safer alternatives for the control of mites and ticks is needed.

Recently, many studies focused on the plant extracts as new acaricidal products because they are biodegradable to non-toxic products and less likely to exhibit resistance [8]. Plant extracts are considered as the secondary metabolites that are not directly involved in the growth, development, or reproduction of the plant [9]. These constituents of plant extracts have already been described by many researches suggesting that they have bactericidal, antifungal, repellent, antiparasitic, and insecticidal properties [8]. In China, *Valeriana fauriei* has been used for the traditional medicine in the treatment of anxiety, insomnia, and sedation [10]. Several researchers have reported that the essential oils derived from *Valeriana* spp. exhibited the insecticidal activities against mosquitos including *Aedes aegypti*, *A. albopictus, Anopheles stephensi*, *A. culicifacies*, and *Culex quinquefasciatus* [11], and a nematode *Bursaphelenchus xylophilus* [12].

Although botanical insecticides are effective, their high molecular reactivity can be a limitation for manufacturing botanical insecticides. To maximize their biological properties, the essential oil and its active constituents need to be changed as the more stable forms. Nanoemulsions have stable colloidal properties with droplet sizes of 20–200 nm, and which contain oil in their outer shell layer and a core portion inside active substances [13]. Because of their high kinetic stability, low viscosity, and optical transparency, nanoemulsions are used for many industrial applications including pharmaceutical, cosmetic, agrochemical, and polymerization fields [13].

In this study, we evaluated the acaricidal activities of *V. fauriei* essential oil and its constituents against *D. farinae*, *D. pteronyssinus*, *H. longicornis*, and *T. putresceantiae* and the color alterations of synanthropic mites. Furthermore, the acaricidal efficiency of the nanoemulsified plant oil components was evaluated using spray method to develop the new strategic acaricides.

Materials and methods

Chemicals

Amitraz (97%) and *N*,*N*-diethyl-*m*-toluamide (DEET) (98%) were purchased from TCI (Tokyo, Japan). Benzyl benzoate (99%), 4,5-dimethylfurfural (97%), furfural (99%), furan (99%), α-guaiene (95%), (−)-α-gurjunene (97%), 5-hydroxymethylfurfural (97%), isovalerate (99%), 2-methylfuran (99%), 5-methylfurfural (99%), methyl 3-methylvalerate (97%), (−)-patchouli alcohol (98%), and viridiflorol (95%) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Mite culture and tick collection

The stock cultures of *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* were separately maintained without exposure to any acaricides over a period of 10 years [14]. Mites were maintained on fry feed no. 1 (Korea Special Feed Meal Co. Ltd., Jeonju, Korea) and dried yeast (1:1 by weight) and reared in the plastic box (15 × 12 × 6 cm) containing 28 g of a sterilized diet. The rearing cage was kept in temperature-controlled incubators at 26 ± 1 °C and 70 ± 5% relative humidity in continuous darkness within a plastic container (20 × 20 × 20 cm) that contained a supersaturated NaCl solution to prevent the escape of mites and to maintain relative humidity. *Haemaphysalis longicornis* nymphs were collected at Seogwipo city, Jeju Island, South Korea.

Sample preparation and steam distillation extraction (SDE)

The roots of *Valeriana fauriei* (3 kg) were supplied from an herbal market in Jeonju, South Korea. The samples were washed three times with distilled water and dried in an oven at 38 °C. After 6 h, the dried samples finely homogenized with a grinder. Hexane was used as the extraction solvent. The *V. fauriei* root was diluted with distilled water in a flask and heated with 4 h. After the extraction finished, anhydrous sodium sulfate was added to the extract to remove remain water. The residual solvent of the extract was removed with a rotary evaporator (EYELA auto jack NAJ-100, Tokyo, Japan) at 35 °C and stored at 4 °C.

Solvent extraction (SE)

The powdered sample was placed in a 5000 mL glass flask with hexane (1500 mL). The extraction was performed on a shaking incubator (Edun, Seongnam, South Korea) at 230 rpm and 26 °C for 48 h. The extract was filtered to remove residues, and the residual solvent was removed with a rotary evaporator at 35 °C and stored at 4 °C.

Supercritical fluid extraction (SFE)

SFE was carried out as described by Lee et al. [15]. A supercritical fluid extractor (SCFE-0500, Ilshin autoclave,

Daejeon, Korea) was used to obtain the extract of *V. fauriei* using supercritical CO_2 at a temperature of 40–50 °C and a pressure of 40–400 bar for 2 h. A flow rate of supercritical CO_2 was approximately 60 mL/min.

Gas chromatography-mass spectrometry (GC–MS)

The *V. fauriei* essential oils obtained by SDE, SE, and SFE were analyzed on Agilent-6890 GC system with Agilent-5973 MS operating in electron ionization mode at 70 eV. The system was equipped with a DB-5 fused silica capillary column (30 m × 0.25 mm i.d., J&W Scientific, Folsom, CA, USA). The injection temperature was set at 50 °C, which was gradually increased to 210 °C at 2 °C/min. Helium was used as carrier gas at constant flow rate of 0.8 ml/min. The ion source temperature was 230 °C. Mass spectra (m/z) were set to scan a range of 20–400 amu. The constituents of three *V. fauriei* essential oils were identified by comparing with standard compounds and mass spectra library [16].

Preparation of nanoemulsion

The oil-in-water nanoemulsion was prepared by using high-energy method and modified by the method of Sugumar et al. [17]. Briefly, emulsification was formulated by adding an organic phase to an aqueous phase. 4,5-Dimethylfurfural was mixed with Tween 80 (nonionic surfactant) in ratio of 1:2 (v/v) as an organic phase, and glycerol (5%, v/v) was added to distilled water as aqueous phase. A coarse emulsion was prepared by blending an organic and aqueous phase using a magnetic stirrer (400 rpm) for 20 min at 40 °C. Nanoemulsion was formed by passing the coarse emulsion through a 20 kHz ultrasonic processor (VCX750, Sonics, USA) with a power output of 750 W.

Nanoemulsion characterization

Particle size as polydispersity index (PDI) of the nanoemulsion were determined by a zeta potential and particle size analyzer (ELSZ-2000, Otsuka Electronics Co., Ltd., Osaka, Japan) at 25 °C. Sample was dispersed in distilled water in a ratio of 1:10. All results were obtained by measuring in triplicate and expressed as the mean ± standard deviation.

Contact + fumigant filter paper bioassay

Contact + fumigant filter paper bioassay was used to measure the lethality and color alteration to *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*, which was modified to the description by Park and Lee [14]. Concentrations of each constituent in descending order (110, 55, 27.5, 13.75, 6.88, and 3.44 μg/cm^2) were applied to 3.5 cm diameter filter paper (Whatman No. 1, Maidstone, UK). The filter paper was dried at room temperature. After 10 min, each filter paper was placed in the bottom of a petri dish (3.5 cm i.d. × 1.0 cm deep; SPL life science, Pocheon, South Korea). Each group of 25–30 *D. farinae*, *D. pteronyssinus*, and *T. putersceantiae* was separately placed in the petri dish and covered with a lid, which wrapped with Bemis Parafilm M (Neenah, WI). The systems were kept in darkness at 27 ± 1 °C and 78% relative humidity at 24 h. Benzyl benzoate and DEET were used as positive control. Negative control consisted of 50 μL of ethanol only. The color alteration of *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* were determined using a contact + fumigant filter paper bioassay and visualized by optical microscopy (× 100; Olympus, Japan). All treatments were replicated 5 times.

Packet bioassay

The packet bioassay was applied to measure the lethality of *V. fauriei* essential oil and its constituents against *H. longicornis*, which was modified from the description of Godara et al. [18]. Six formulations with decreasing concentrations (110.00, 55.00, 27.50, 13.75, 6.88, and 3.44 μg/cm^2) of each constituent dissolved in 200 μL of ethanol were applied to 5.0 × 10.0 cm filter paper. The filter paper was dried at room temperature at 10 min. Dried each filter paper was folded in half and sealed with bulldog clips on both sides. The packet into which 20 *H. longicornis* larvae were dropped was sealed with a bulldog clip. The systems were kept in darkness at 27 ± 1 °C and 80% relative humidity at 24 h. Amitraz was used as positive control. Negative control consisted of 50 μL of ethanol only. All treatments were replicated 5 times.

Spray bioassay

The acaricidal efficacy of 4,5-dimethylfurfural as emulsion dissolved in ethanol and nanoemulsion against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* was measured by direct spray application method modified by Park and Lee [14]. Each group of 25–30 *D. farinae*, *D. pteronyssinus*, and *T. putersceantiae* was placed in the bottom of petri dish (3.5 cm i.d. × 1.0 cm deep). Each test sample was sprayed one time successively at 15 cm upwards onto the 3.5 cm diameter filter paper. After dried at 20 min, each petri dish was covered with a lid and wrapped with Bemis Parafilm M. The systems were kept in darkness at 27 ± 1 °C and 78% relative humidity at 24 h. All treatments were replicated 5 times.

Statistical analysis

All data were corrected by Abbott's formula [19]. The 50 and 90% lethal dose (LD_{50} and LD_{90}) values were calculated by probit analysis. Relative toxicity (RT) was expressed based on the ratio of LD_{50} values of amitraz and DEET to LD_{50} values of each compound,

as described previously [20]. The statistical difference between closed and open container bioassay was analyzed by Student's t test. SPSS version 12 software (SPSS Inc., Chicago, IL, USA) was used to analyze all data.

Results

Acaricidal effects of *V. fauriei* essential oils obtained by SDE, SE, and SFE

The mean yields of *Valeriana fauriei* essential oils obtained by steam distillation (SDE), solvent extraction (SE), and supercritical fluid extraction (SFE) were 0.67%, 0.83%, and 1.84%, respectively. The acaricidal effects of *V. fauriei* essential oils obtained by SDE, SE, and SFE against *D. farinae*, *D. pteronyssinus*, *H. longicornis*, and *T. putrescentiae* were compared with the positive control (Table 1). Based on the LD_{50} values, the *V. fauriei* essential oil (LD_{50}, 15.15, 13.64, and 10.14 μg/cm^2) obtained by SDE was 1.28–1.83-fold more active than DEET (20.26, 17.40, and 18.54 μg/cm^2) against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*, respectively. However, the essential oil obtained by SE and SFE did not show the acaricidal activities against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*. The *V. fauriei* essential oil obtained by SDE, SE, and SFE also did not show the acaricidal activities against *H. longicornis*.

GC–MS analysis of *V. fauriei* essential oils obtained by SDE, SE, and SFE

The components of *V. fauriei* essential oil obtained by SDE, SE, and SFE were investigated by GC–MS (Table 2). *V. fauriei* essential oil obtained by SDE yielded 17 compounds that represented 98.89% of the total oil, with viridiflorol (17.15%), isovalerate (12.04%), β-gurjunene (10.45%), α-guaiene (9.85%), α-patchoulene (6.87%), methyl 3-methylvalerate (6.81%), patchouli alcohol (6.44%), α-gurjunene (5.98%), and 5-methylfurfural (5.41%) being the major compounds. In *V. fauriei* essential oil obtained by SE, a total of 19 components were identified, which represented 100% of the total oil. The main compounds were 1-ethyl-4,4-dimethyl-2-cyclohexen-1-ol (19.06%), γ-sitosterol (18.80%), baldrinal (11.36%), patchouli alcohol (7.17%), and 8-acetyl-5,5-dimethylbicyclo[2.2.2]octan-2-one (7.10%). In the case of *V. fauriei* essential oil obtained by SFE, the main compounds were found to be 1-ethyl-4,4-dimethyl-2-cyclohexen-1-ol (15.77%), γ-sitosterol (13.20%), baldrinal (11.24%), allyl valerate (10.08%), 1-cyclohexyl-4,4-diethoxy-2-butyn-1-one (6.86%), 2,2-dicyclohexylmalononitrile (5.72%), and S-propyl pentanethioate (5.30%), which represented 97.77% of the total oil.

Acaricidal effects of constituents of *V. fauriei* essential oil obtained by SDE

The acaricidal effects of 7 commercial constituents [α-guaiene, (−)-α-gurjunene, isovalerate, 5-methylfurfural, methyl 3-methylvalerate, (−)-patchouli alcohol, and viridiflorol] against *D. farinae*, *D. pteronyssinus*, *H. longicornis*, and *T. putrescentiae* were compared with positive control (Table 3). Based on the LD_{50} values, 5-methylfurfural (11.87, 11.00, and 8.59 μg/cm^2) was 1.58–2.16-fold more active than DEET (20.26, 17.40, and 18.54 μg/cm^2) against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*, respectively, followed by isovalerate (13.75, 15.71, and 11.23 μg/cm^2). However, isovalerate and 5-methylfurfural did not show the acaricidal activities against *H. longicornis*. α-Guaiene, (−)-α-gurjunene, methyl 3-methylvalerate, (−)-patchouli alcohol, and viridiflorol also did not show the acaricidal activities against *D. farinae*, *D. pteronyssinus*, *H. longicornis*, and *T. putrescentiae*.

Acaricidal effects of 5-methylfurfural analogues

To explore the structural relationships between 5-methylfurfural and the analogues for the acaricidal activities against *D. farinae*, *D. pteronyssinus*, *H. longicornis*, and *T. putrescentiae*, furan, 2-methylfuran, furfural, 4,5-dimethylfurfural, and 5-hydroxymethylfurfural were selected as 5-methylfurfural analogues for the testing (Table 4). Based on the LD_{50} values, 4,5-dimethylfurfural showed the most toxic activities among the analogues against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* (9.95, 9.91, and 7.12 μg/cm^2), respectively, followed by furfural (12.94, 13.25, and 10.36 μg/cm^2), 5-hydroxymethylfurfural (53.82, 48.71, and 57.58 μg/cm^2) and 2-methylfuran (58.84, 57.02, and 39.71 μg/cm^2). However, furan did not show the acaricidal activities against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*. The all 5-methylfurfural analogues did not show the acaricidal activities against *H. longicornis*. The color alterations by 5-methylfurfural and its analogues were evaluated using the contact + fumigant filter paper bioassay against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* (Fig. 1). After 24 h of treatment, *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* treated with furfural, 5-methylfurfural, and 4,5-dimethylfurfural exhibited changes in body color to red brown. However, *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* treated with benzyl benzoate and DEET did not exhibit the color change.

Table 1 Acaricidal activities of *Valeriana fauriei* essential oils obtained by SDE, SE and SFE against *D. farinae*, *D. pteronyssinus*, *H. longicornis* and *T. putrescentiae*

Samples	Insects	Bioassays	LD_{50} (95% CI)	LD_{90} (95% CI)	Slope ± SE	χ^2 (df, *p*)	RTD	RTA
V. fauriei SDE oil	*D. farinae*	Contact + fumigant (μg/cm^2)	15.15 (11.90–19.28)	38.04 (28.22–62.13)	3.21 ± 0.50	3.072 (4, 0.546)	1.3	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	13.64 (10.87–17.31)	32.12 (24.22–51.32)	3.47 ± 0.56	1.624 (4, 0.824)	1.3	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	10.14 (8.87–11.70)	17.97 (14.93–24.57)	5.16 ± 0.81	2.232 (4, 0.693)	1.8	–
V. fauriei SE oil	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
V. fauriei SFE oil	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
Amitraz	*D. farinae*	Contact + fumigant (μg/cm^2)	–[a]	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	–	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	23.83 (18.67–30.46)	64.18 (47.12–105.32)	2.98 ± 0.44	3.379 (4, 0.497)	–	1.0
	T. putrescentiae	Contact + fumigant (μg/cm^2)	–	–	–	–	–	–
Benzyl benzoate	*D. farinae*	Contact + fumigant (μg/cm^2)	12.11 (10.49–14.03)	22.94 (18.86–31.76)	4.62 ± 0.71	3.660 (4, 0.454)	1.7	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	11.09 (9.62–12.77)	20.45 (17.01–27.64)	4.83 ± 0.73	3.319 (4, 0.506)	1.6	–
	H. longicornis	Packet (mg/ml)	–	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	9.95 (8.49–11.48)	18.08 (15.15–24.05)	4.94 ± 0.77	1.016 (4, 0.907)	1.9	–
DEET	*D. farinae*	Contact + fumigant (μg/cm^2)	20.26 (17.12–24.49)	44.14 (34.22–68.35)	3.79 ± 0.59	2.401 (4, 0.662)	1.0	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	17.40 (15.12–20.31)	31.77 (25.98–45.00)	4.90 ± 0.79	1.301 (4, 0.861)	1.0	–
	H. longicornis	Packet (mg/ml)	–	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	18.54 (16.01–21.85)	35.24 (28.39–51.39)	4.59 ± 0.74	2.226 (4, 0.694)	1.0	–

RTD relative toxicity = LD_{50} value of DEET/LD_{50} value of each compound

RTA relative toxicity = LD_{50} value of amitraz/LD_{50} value of each compound

[a] –, not tested

Characterization of 4,5-dimethylfurfural nanoemulsion

Particle size as PDI of 4,5-dimethylfurfural nanoemulsion was given in Fig. 2. Mean droplet size and PDI analysis showed that nanoemulsion of 4,5-dimethylfurfural exhibited small mean diameter (161.3 ± 32.3 nm) and low polydispersity (0.137 ± 0.031) which means narrow particle size distribution (PDI < 0.2).

Acaricidal effect and color alteration of 4,5-dimethylfurfural nanoemulsion

The acaricidal effect of 4,5-dimethylfurfural nanoemulsion was evaluated by spray bioassay and compared with its emulsion dissolved in ethanol (Table 5). Based on the LD_{50} values, the 4,5-dimethylfurfural nanoemulsion (LD_{50}, 7.24, 6.87, and 5.59 μg/cm^2) was 1.27–1.44-fold

Table 2 GC–MS analysis of *Valeriana fauriei* essential oils by SDE, SE and SFE

No.	Compounds	RI	Relative amount (%)		
			Steam	Solvent	Supercritical
1	Methyl 3-methylvalerate	820	6.81	–	–
2	Isovalerate	811	12.04	–	–
3	5-methylfurfural	920	5.41	–	–
4	Limonene	1033	–[a]	2.27	–
5	β-hydroxyisovaleric acid	966	–	–	2.25
6	Bornyl acetate	1277	–	1.21	–
7	Allyl valerate	974	–	–	10.08
8	α-santalene	1420	1.19	–	–
9	α-bergamotene	1431	0.97	–	–
10	β-gurjunene	1403	10.45	–	–
11	β-caryophyllene	1494	4.66	3.71	–
12	Seychellene	1460	4.75	4.66	2.08
13	α-gurjunene	1419	5.98	2.87	–
14	β-selinene	1436	–	1.04	–
15	α-patchoulene	1456	6.87	2.94	–
16	(+)-cyclosativene	1125	1.23	–	–
17	2,8,8-trimethyl-4-methylene-2-vinylbicyclo[5.2.0]nonane	1407	2.69	–	–
18	α-guaiene	1490	9.85	1.12	–
19	α-panasinsene	1416	1.52	1.60	–
20	Viridiflorol	1754	17.15	–	–
21	β-eudesmol	1593	0.88	–	–
22	Patchouli alcohol	1659	6.44	7.17	4.82
23	Baldrinal	1689	–	11.36	11.24
24	Palmitic acid	1968	–	–	3.18
25	1-ethyl-4,4-dimethyl-2-cyclohexen-1-ol	1147	–	19.06	15.77
26	3-Acetoxycinnamic acid	1737	–	3.33	–
27	6-hydroxy-5,7,8-trimethyl-2-chromanone	1952	–	–	2.95
28	Methyl 3-acetoxy-3-hydroxy-2-methylpropanoate	1150	–	–	1.68
29	4-carvomenthenol	2458	–	–	2.28
30	Artemisia ketone	1042	–	1.59	–
31	8-acetyl-5,5-dimethyl-bicyclo[2.2.2]octan-2-one	1464	–	7.10	–
32	1-cyclohexyl-4,4-diethoxy-2-butyn-1-one	1717	–	–	6.86
33	2,6-dimethyl-6-nitro-2-hepten-4-one	1334	–	2.41	–
34	2,2-dicyclohexylmalononitrile	2045	–	–	5.72
35	S-propyl pentanethioate	1139	–	2.85	5.30
36	(−)-praeruptorin B	3097	–	4.91	2.30
37	1,6-dibromohexane	1210	–	–	2.14
38	2,3,7-trimethyl-3-vinyl-oct-6-enoic acid	1496	–	–	3.11
39	(+)-α-tocopherol	3149	–	–	2.81
40	γ-sitosterol	2731	–	18.80	13.20
Major grouped compounds					
Acid			12.04	6.18	13.84
Aldehydes			5.41	11.36	11.24
Aliphatic ester			6.81	–	–
Alkanes			3.92	–	–
Ketones			–	1.59	–
Monoterpene alcohol			–	19.06	18.05
Monoterpene esters			–	3.62	11.76

Table 2 (continued)

No.	Compounds	RI	Relative amount (%)		
			Steam	Solvent	Supercritical
	Monoterpene ketone		–	–	–
	Monoterpene hydrocarbons		–	2.27	–
	Sesquiterpene alcohols		47.64	7.17	7.77
	Sesquiterpene esters		–	–	6.86
	Sesquiterpene ethers		–	7.10	–
	Sesquiterpenene hydrocarbons		23.07	17.94	2.08
	Sesquiterpenene nitrile		–	–	5.72
	Triterpenoids		–	18.80	16.01
	Pyranocoumarins		–	4.91	2.30
Total (%)			98.89	100.00	97.77
Yield (%)			0.66	0.84	2.21

RI retention index

[a] Not detected

more active than the emulsion dissolved in ethanol against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*, respectively. The color alterations by 4,5-dimethylfurfural nanoemulsion were evaluated using the spray bioassay (Fig. 3). After 24 h of treatment, *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* treated with the nanoemulsion exhibited changes in body color to red brown.

Discussion

In this study, the acaricidal activities of *V. fauriei* essential oil obtained by three extraction methods (SDE, SE, and SFE) and its constituents were found. The essential oil obtained by SDE affected the highest acaricidal activity among the tested oils against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*, despite the lowest mean yield. Unfortunately, the oil did not show any toxic response against *H. longicornis*. The differential susceptibility of the essential oils to tested mites and ticks may be influenced by biological factors (body size, weight, external structure, etc.) and biochemical properties (detoxification enzyme activity such as esterases, cytochrome P450 monooxygenases, and glutathione-S-transferases). According to previous studies, the *Coriandrum sativum* essential oil obtained by SDE exhibited the higher acaricidal activities against *T. putrescentiae* (LD_{50}; 19.29 μg/cm^2) than the essential oils obtained by SE and SFE [15]. In contrast, the *Cinnamomum cassia* essential oil obtained by SE revealed the higher acaricidal activities against *T. putrescentiae* (LD_{50}; 2.60 μg/cm^2) than the essential oils obtained by SDE and SFE [21]. These results indicated that the acaricidal activity varied with the extraction methods of essential oil. To our knowledge, this study is the first report on the acaricidal activities of *V. fauriei* essential oil against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*. It is suggested that *V. fauriei* essential oil obtained by SDE is potent for the development of effective and efficient natural acaricide for the control of the synanthropic mites.

The SDE is generally used for extraction to volatile compounds, especially monoterpenes, which exhibit the acaricidal activity [22]. However, the *V. fauriei* essential oils showed different results from those of previous studies. The most abundant component in the *V. fauriei* essential oils obtained by SDE was viridiflorol (17.15%), which is one of sesquiterpene compounds. This essential oil exhibited higher sesquiterpene composition (70.71%) than those obtained by the SE and SFE (32.21% and 22.43%, respectively). There are many reports on the abundance of sesquiterpenes in the essential oils of *Valeriana* spp. The most abundant fraction of the roots and rhizomes of *V. officinalis* was sesquiterpene fraction (70.5%) and its main constituent was valerianol (57.3%) [23]. In the essential oil of *V. sisymbriifolia*, b-atlantone and 14-hydroxy-9-epi-(E)-caryophyllene (16.3%) were the main constituents and oxygenated sesquiterpenes (39.1%) constituted the major portion [24]. These differences of the compositions may be caused by different cultivation conditions, such as climate, season, geographical environment, and growth stage of plants [25].

To explore the active compounds in *V. fauriei* essential oil obtained by SDE, the acaricidal potential of 7 commercial constituents (over 5%) were evaluated by acaricidal experimentation. As a result, 5-methylfurfural and isovalerate had the highest lethality against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*. 5 methylfurfural showed 1.7, 1.6 and 2.2 times more toxic than DEET, and isovalerate showed 1.5, 1.1 and 1.7 times more toxic than DEET against *D. farinae*, *D. pteronyssinus*, and *T.*

Table 3 Acaricidal activities of 7 constituents of *Valeriana fauriei* essential oil obtained by SDE against *D. farinae*, *D. pteronyssinus*, *H. longicornis* and *T. putrescentiae*

Compound	Insect	Bioassay	LD_{50} (95% CI)	LD_{90} (95% CI)	Slope ± SE	χ^2 (df, *p*)	RTD	RTA
Methyl 3-methylvalerate	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
Isovalerate	*D. farinae*	Contact + fumigant (μg/cm^2)	13.75 (10.68–17.58)	36.30 (26.72–60.05)	3.04 ± 0.48	4.261 (4, 0.372)	1.5	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	15.71 (12.42–19.87)	37.55 (28.15–60.44)	3.39 ± 0.54	2.430 (4, 0.657)	1.1	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	11.23 (8.76–14.23)	27.74 (20.73–45.08)	3.27 ± 0.53	2.990 (4, 0.657)	1.7	–
5-methylfurfural	*D. farinae*	Contact + fumigant (μg/cm^2)	11.87 (9.75–14.56)	27.64 (21.06–44.36)	3.49 ± 0.57	1.669 (4, 0.796)	1.7	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	11.00 (9.05–13.41)	24.99 (19.21–39.71)	3.60 ± 0.60	1.729 (4, 0.785)	1.6	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	8.59 (6.47–11.28)	28.07 (19.77–49.41)	2.49 ± 0.38	5.047 (4, 0.283)	2.2	–
(−)-α-gurjunene	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
α-guaiene	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
Viridiflorol	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
(−)-patchouli alcohol	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–

Table 3 (continued)

Compound	Insect	Bioassay	LD_{50} (95% CI)	LD_{90} (95% CI)	Slope ± SE	χ^2 (df, *p*)	RTD	RTA
Amitraz	*D. farinae*	Contact + fumigant (μg/cm^2)	–[a]	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	–	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	23.83 (18.67–30.46)	64.18 (47.12–105.32)	2.98 ± 0.44	3.379 (4, 0.497)	–	1.0
	T. putrescentiae	Contact + fumigant (μg/cm^2)	–	–	–	–	–	–
Benzyl benzoate	*D. farinae*	Contact + fumigant (μg/cm^2)	12.11 (10.49–14.03)	22.94 (18.86–31.76)	4.62 ± 0.71	3.660 (4, 0.454)	1.7	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	11.09 (9.62–12.77)	20.45 (17.01–27.64)	4.83 ± 0.73	3.319 (4, 0.506)	1.6	–
	H. longicornis	Packet (mg/ml)	–	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	9.95 (8.49–11.48)	18.08 (15.15–24.05)	4.94 ± 0.77	1.016 (4, 0.907)	1.9	–
DEET	*D. farinae*	Contact + fumigant (μg/cm^2)	20.26 (17.12–24.49)	44.14 (34.22–68.35)	3.79 ± 0.59	2.401 (4, 0.662)	1.0	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	17.40 (15.12–20.31)	31.77 (25.98–45.00)	4.90 ± 0.79	1.301 (4, 0.861)	1.0	–
	H. longicornis	Packet (mg/ml)	–	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	18.54 (16.01–21.85)	35.24 (28.39–51.39)	4.59 ± 0.74	2.226 (4, 0.694)	1.0	–

RTD relative toxicity = LD_{50} value of DEET/LD_{50} value of each compound

RTA Relative toxicity = LD_{50} value of amitraz/LD_{50} value of each compound

[a] –, not tested

putrescentiae. On the other hand, viridiflorol that was the most abundant compound in the *V. fauriei* SDE oil showed no acaricidal activities in all tested concentrations. Although isovalerate and 5-methylfurfural did not account the high percentage in the essential oil, they have a potential as an alternative of synthetic acaricide because of their effectiveness. Liu et al. [26] reported that isovalerate derived from *Valeriana jatamansi* exhibited stronger lethal toxicity against *Liposcelis bostrychophila* with the LC_{50} value of 426.34 μg/cm^2.

Many potential acaricides derived from plants have been explored for mite control. However, complete elimination of mite allergens (residual mite excrements, dead mites, and eggs) is actually impossible because of their invisible size. These problems led to the development of a new strategies for the control of synanthropic mite allergens. Interestingly, this study showed the color alteration of 5-methylfurfural against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* (Fig. 1). The mechanism of the discoloration could be associated with melanization performed by polyphenol oxidase and tyrosinase. Polyphenol oxidase is the enzyme of the insect innate immune system by producing melanin, which prevents the introduction of outside substances [27]. Tyrosinase plays a role in protection of UV damage and initiates melanization by hydroxylating tyrosine to (dopa) and oxidizing the (dopa) to dopaquinone [28]. Similar to this study, plumbagin, naphthazarin, dichlone, 2-bromo-1,4-naphthoquinone [29], 2,3-dihydroxybenzaldehyde [30], and citral [14] were reported as color alteration agents. In this regard, the red brown color intensity was not correlated with the toxicity of treated components.

To evaluate the structure–activity relationships of 5-methylfurfural and its structural analogues, furan, 2-methylfuran, furfural, 4,5-dimethylfurfural, and 5-hydroxymethylfurfural were tested. The SAR was mainly based upon by bringing about difference of substituents on furan ring. In the contact + fumigant bioassay, the acaricidal activities of the structural analogues containing a methyl (CH_3) functional group (5-methylfurfural, 4,5-dimethylfurfural, and 2-methylfuran) were more toxic than those of hydroxymethyl functional group (5-hydroxymethylfurfural) or no functional group (furan). The color alterations of *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* were also observed when treated with the structural analogues containing a methyl functional group (5-methylfurfural and 4,5-dimethylfurfural) except for 2-methylfuran. Oh et al. [31] showed that acetophenone derivatives containing a methyl group exhibited strong acaricidal activity against *D. farinae* and *D. pteronyssinus*. Furthermore, Yang et al. [30] reported that the number of methyl functional groups of

Table 4 Acaricidal activities of 5-methyhlfurfural analogues against *D. farinae*, *D. pteronyssinus*, *H. longicornis* and *T. putrescentiae*

Compound	Insect	Bioassay	LD_{50} (95% CI)	LD_{90} (95% CI)	Slope ± SE	χ^2 (df, *p*)	RTD	RTA
Furan	*D. farinae*	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	> 110.00	–	–	–	–	–
2-methylfuran	*D. farinae*	Contact + fumigant (μg/cm^2)	58.84 (47.55–72.92)	119.38 (92.62–184.70)	4.17 ± 0.72	0.404 (4, 0.982)	0.3	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	57.02 (45.49–71.60)	127.56 (96.83–202.80)	3.67 ± 0.60	1.179 (4, 0.882)	0.3	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	39.71 (31.96–49.61)	84.53 (64.73–133.05)	3.91 ± 0.65	2.338 (4, 0.674)	0.5	–
Furfural	*D. farinae*	Contact + fumigant (μg/cm^2)	12.94 (10.50–15.88)	24.95 (19.65–37.72)	4.49 ± 0.79	0.648 (4, 0.958)	1.6	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	13.25 (10.70–16.42)	26.96 (20.92–41.66)	4.15 ± 0.71	0.513 (4, 0.972)	1.3	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	10.36 (7.95–13.56)	31.57 (22.35–55.33)	2.65 ± 0.40	2.122 (4, 0.713)	1.8	–
4,5-dimethylfurfural	*D. farinae*	Contact + fumigant (μg/cm^2)	9.95 (8.60–11.46)	16.30 (13.62–23.48)	5.97 ± 1.22	0.386 (4, 0.984)	2.0	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	9.91 (8.43–11.61)	17.87 (14.56–26.53)	5.00 ± 0.96	1.955 (4, 0.744)	1.8	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	7.12 (5.67–8.92)	15.91 (12.12–25.09)	3.67 ± 0.60	1.187 (4, 0.880)	2.6	–
5-hydroxymethylfurfural	*D. farinae*	Contact + fumigant (μg/cm^2)	53.82 (43.95–65.49)	98.31 (78.46–146.24)	4.90 ± 0.90	1.226 (4, 0.874)	0.4	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	48.71 (38.98–60.46)	103.07 (79.73–158.01)	3.94 ± 0.65	2.824 (4, 0.398)	0.4	–
	H. longicornis	Packet (mg/ml)	> 50.00	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	57.58 (48.58–67.05)	101.58 (84.45–139.76)	5.20 ± 0.91	4.058 (4, 0.398)	0.3	–
Amitraz	*D. farinae*	Contact + fumigant (μg/cm^2)	–[a]	–	–	–	–	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	–	–	–	–	–	–
	H. longicornis	Packet (mg/ml)	23.83 (18.67–30.46)	64.18 (47.12–105.32)	2.98 ± 0.44	3.379 (4, 0.497)	–	1.0
	T. putrescentiae	Contact + fumigant (μg/cm^2)	–	–	–	–	–	–
Benzyl benzoate	*D. farinae*	Contact + fumigant (μg/cm^2)	12.11 (10.49–14.03)	22.94 (18.86–31.76)	4.62 ± 0.71	3.660 (4, 0.454)	1.7	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	11.09 (9.62–12.77)	20.45 (17.01–27.64)	4.83 ± 0.73	3.319 (4, 0.506)	1.6	–
	H. longicornis	Packet (mg/ml)	–[a]	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	9.95 (8.49–11.48)	18.08 (15.15–24.05)	4.94 ± 0.77	1.016 (4, 0.907)	1.9	–
DEET	*D. farinae*	Contact + fumigant (μg/cm^2)	20.26 (17.12–24.49)	44.14 (34.22–68.35)	3.79 ± 0.59	2.401 (4, 0.662)	1.0	–
	D. pteronyssinus	Contact + fumigant (μg/cm^2)	17.40 (15.12–20.31)	31.77 (25.98–45.00)	4.90 ± 0.79	1.301 (4, 0.861)	1.0	–
	H. longicornis	Packet (mg/ml)	–	–	–	–	–	–
	T. putrescentiae	Contact + fumigant (μg/cm^2)	18.54 (16.01–21.85)	35.24 (28.39–51.39)	4.59 ± 0.74	2.226 (4, 0.694)	1.0	–

RTD relative toxicity = LD_{50} value of DEET/LD_{50} value of each compound

RTA relative toxicity = LD_{50} value of amitraz/LD_{50} value of each compound

[a] –, not tested

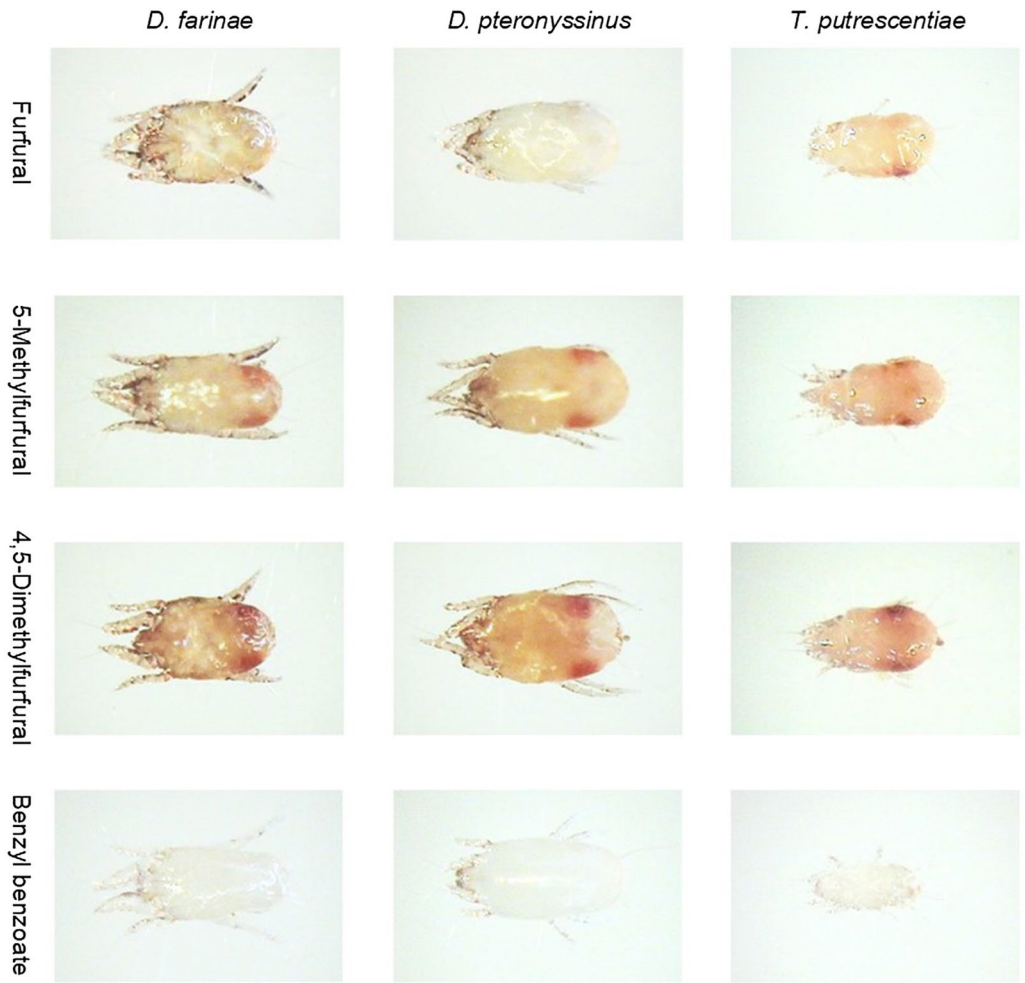

Fig. 1 Color alteration of *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* treated with furfural, 5-methylfurfural, 4,5-dimethylfurfural and DEET

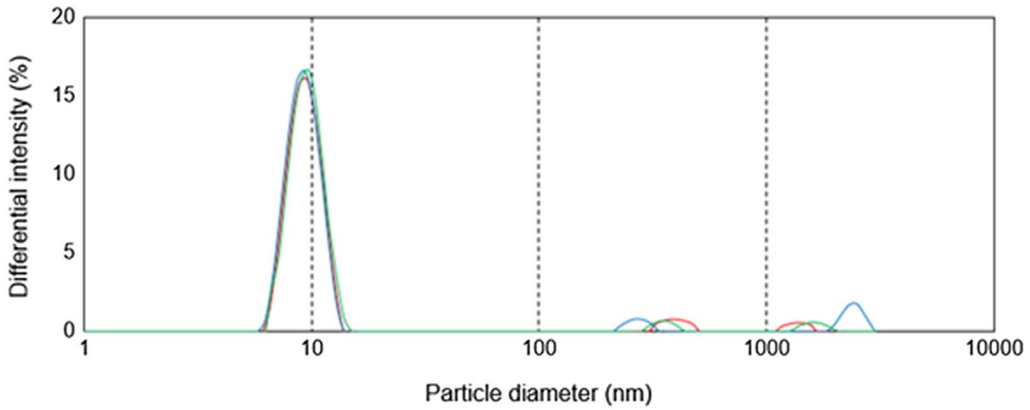

Fig. 2 Particle size distribution of 4,5-dimethylfurfural nanoemulsion. Mean droplet size, 161.3 ± 32.3 nm; Polydispersity index, 0.137 ± 0.031

Table 5 Acaricidal activities of 4,5-dimethylfurfural nanoemulsion against *D. farinae*, *D. pteronyssinus* and *T. putrescentiae* using spray bioassay

Compound	Insect	LD_{50} (μg/cm^2; 95% CI)	LD_{90} (μg/cm^2; 95% CI)	Slope ± SE	χ^2 (df, *p*)
4,5-dimethylfurfural nanoemulsion	*D. farinae*	7.24 (5.84–8.71)	15.96 (12.80–22.50)	3.74 ± 0.57	3.524 (4, 0.474)
	D. pteronyssinus	6.87 (5.51–8.28)	15.29 (12.24–21.59)	3.69 ± 0.56	3.860 (4, 0.425)
	T. putrescentiae	5.59 (4.41–6.94)	14.39 (10.97–22.09)	3.12 ± 0.47	3.710 (4, 0.447)
4,5-dimethylfurfural emulsion dissolved in ethanol	*D. farinae*	9.95 (8.60–11.46)	16.30 (13.62–23.48)	5.97 ± 1.22	0.386 (4, 0.984)
	D. pteronyssinus	9.91 (8.43–11.61)	17.87 (14.56–26.53)	5.00 ± 0.96	1.955 (4, 0.744)
	T. putrescentiae	7.12 (5.67–8.92)	15.91 (12.12–25.09)	3.67 ± 0.60	1.187 (4, 0.880)

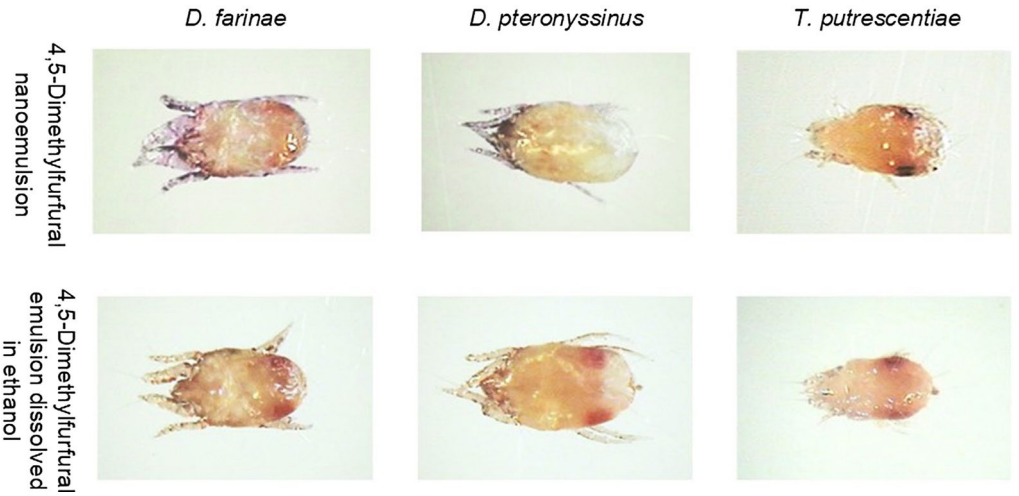

Fig. 3 Color alteration of *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* treated with 4,5-dimethylfurfural emulsion dissolved in ethanol and nanoemulsion

benzaldehyde influenced the acaricidal activity against *D. farinae*, *D. pteronyssinus*, and *H. longicornis*. These results seem to be attributed the difference in the existence of a methyl functional group.

One of the issues for practical uses of the essential oil or its plant-derived compound as commercial pesticides is its short lasting for acaricidal effect [17]. Furthermore, these plant-derived compounds are known to have poor water solubility. To overcome these problems, formulation into nanoemulsion has been developed. Nanoemulsion is also considered for enhancing water solubility and bioavailability of organic compounds. For these reasons, several studies trying to increase the bioactivities of nanoemulsions have been reported [32, 33]. This study also showed that the nanoemulsion of 4,5-dimethylfurfural, which was the most active compound among 5-methylfurfural derivatives, showed more effective acaricidal activity than the emulsion dissolved in ethanol against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae*. Regarding the mite color alteration, there was no difference between the ethanol-dissolved emulsion and nanoemulsion. 5-Methylfurfural and isovalerate from V. fauriei essential oil may suggest a new concept of acaricides due to the potential indicating feature by color alteration of synanthropic mites.

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Authors' contributions
S-AC carried out the experiments, prepared most of the data, and wrote the primary paper; JHP rewrote the paper; HSL proposed the key idea of this paper, designed the experiments, managed the research process, and wrote the paper; JHL managed the research process and rewrote the paper. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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