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Anticonflict effects of lavender oil and identification of its active constituents

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Abstract

The pharmacological effects of lavender oil were investigated using two conflict tests in ICR mice, and then the active constituents were identified. Lavender oil produced significant anticonflict effects at 800 and 1600 mg/kg in the Geller conflict test and at 800 mg/kg in the Vogel conflict test, suggesting that the oil has an anti-anxiety effect. Analysis using GC/MS revealed that lavender oil contains 26 constituents, among which α-pinene (ratio, 0.22%), camphene (0.06%), β-myrcene (5.33%), *p*-cymene (0.3%), limonene (1.06%), cineol (0.51%), linalool (26.12%), borneol (1.21%), terpinene-4-ol (4.64%), linalyl acetate (26.32%), geranyl acetate (2.14%) and caryophyllene (7.55%) were identified. We examined the effects of linalool, linalyl acetate, borneol, camphene, cineol, terpinen-4-ol, α-pinene and β-myrcene using the Geller and Vogel conflict tests in ICR mice. Cineol, terpinen-4-ol, α-pinene and β-myrcene did not produce any significant anticonflict effects in the Geller test. Linalyl acetate did not produce any significant anticonflict effects in either test. Both borneol and camphene at 800 mg/kg produced significant anticonflict effects in the Geller, but not in the Vogel conflict test. Linalool, a major constituent of lavender oil, produced significant anticonflict effects at 600 and 400 mg/kg in the Geller and Vogel tests, respectively, findings that were similar to those of lavender oil. Thus, we concluded that linalool is the major pharmacologically active constituent involved in the anti-anxiety effect of lavender oil.

Keywords: Aromatherapy; Lavender oil; Linalool; Anticonflict effects; Anxiety; Mice

1. Introduction

Various mental disorders have traditionally been treated with plant-derived essential oils (EOs). The medicinal use of EOs that originated in ancient Egypt has continued until the present, and aromatherapy (Tisserand, 1993) has recently undergone a worldwide resurgence. Yet, although EOs might provide a therapeutic alternative to Western medicine (Perry and Perry, 2006), the lack of a scientific basis for their effectiveness remains an obstacle (Lis-Balchin, 1997). The long history of EOs in therapy suggests that they may indeed be effective. The aroma of EOs is believed to be important for their effectiveness in treating various illnesses. However, we believe that an EO aroma alone is insufficiently potent to treat illnesses due to rapid adaptation to odorants (Kurahashi and Menini, 1998). Therefore, we surmised that EOs pharmacologically affect brain functions (i.e. psychoactive actions), a hypothesis that our previous studies support (Umezu, 1999a, 2000; Umezu et al., 2001, 2002; Umezu and Morita, 2003).

We demonstrated that rose oil extracted from rose flowers, possesses anticonflict effects, suggesting that this oil has anti-anxiety properties (Umezu, 1999a). We subsequently demonstrated that the effects of rose oil arise from two of its constituents, namely 2-phenethyl alcohol and citronellol (Umezu et al., 2002). An outstanding issue that remains to be resolved is whether only rose oil and its constituents possess anticonflict effects, given that aromatherapy practitioners have claimed that many EOs possess anti-anxiety effects (Tisserand, 1993). Other studies have found that some EOs and their constituents produce anti-anxiety like effects (Delaveau et al., 1989; Lehrner et al., 2005; Vale et al., 1999; do Vale et al., 2002; Viana et al., 2000; Pultrini et al., 2006).

We found that oil extracted from lavender flowers, produces an anticonflict effect in the Geller conflict test in ICR mice (Umezu, 2000), thus prompting the present study. Lavender oil

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contains many constituents, some of which are also found in rose oil. Thus, one or more lavender oil constituents might possess anti-anxiety effects.

The present study first confirmed the anticonflict effects of lavender oil using two conflict tests in ICR mice, and then analyzed its constituents using GC/MS. We examined the effects of the identified constituents in the same manner and discovered a new compound that possesses an anti-anxiety like effect.

2. Materials and methods

2.1. Animals

Male ICR mice (Clea Japan, Tokyo) aged 7–10 weeks at the start of each experiment, were housed in Plexiglas cages (10 mice/cage) with a stainless steel mesh top and excelsior bedding (Clea Japan). The cages were placed in a room artificially illuminated by fluorescent lamps on a 12L:12D schedule (Light period: 0700–1900 h), at a temperature of 25±1 °C.

All animal experiments proceeded in accordance with the Ethics Committee for Experimental Animals of the National Institute for Environmental Studies, Japan.

2.2. Chemicals

We used natural oil extracted from lavender flowers (*Lavandula officinalis*) by Maggie Tisserand Ltd. (Brighton, UK).

The authentic standards were camphene, β-myrcene, *p*-cymene, linalool, linalyl acetate (Nacalai Tesque, Kyoto), borneol, geranyl acetate (Wako Pure Chem. Ind., Osaka), α-pinene, limonene, cineol (Sigma-Aldrich, Tokyo) and terpinene-4-ol (Tokyo Kasei Ind., Tokyo). The lavender oil and authentic standards were diluted with olive oil and then injected intraperitoneally in a volume of 1 ml/100 g body weight.

2.3. The Geller conflict test

Animals were trained under a MULT FR20/FR20-punishment schedule of food reinforcement, which was a modification (Umezu et al., 1997; Umezu, 1999a, 2000) of the method established by Geller and Seifter (1960). The schedule consisted of four pairs of alternating safe and alarm periods of 5 min each for 40 min. During the safe period, lever pressing by the mouse was reinforced by food pellets at FR20 without an electric shock. During the alarm period, which was indicated by a warning stimulus (tone signal: 500 Hz, 90 dB), every 20th lever press was punished by an electric shock (50–90 V, ca. 0.3 mA, 50 Hz AC, duration=0.3 s). After establishing stable baseline response rates for the safe and alarm periods, response rates during the safe and alarm periods were high and low, respectively. Subsequent challenge tests were applied at 3–4 day intervals in which lavender oil or its constituents were administered 20 min before the start of the test session. Response rates during the safe and alarm periods were separately recorded. On non-experimental days, the animals were trained without treatment, and the stability of the behavioral baseline was checked. Daily access to food was limited to maintain a state of food deprivation.

The apparatus for the Geller conflict test (Umezu, 1999a, 2000; Umezu et al., 1997, 2002) consisted of an operant chamber, a schedule controller and a data recorder (GT-8510, GT-8005 and GT-7715, respectively; O'hara and Co., Tokyo). The chamber was constructed of acrylic fiber board and aluminum panels with a dimension of 80 (W)×90 (D)×100 (H) mm. A stainless steel lever was set vertically in a sidewall of the chamber and a saucer for food pellets was positioned in the same wall. The floor consisted of a stainless steel grid, wired to pass an electric current in accordance with the conflict schedule. A speaker for presenting warning stimuli was placed in the center of the chamber ceiling.

2.4. The Vogel conflict test

We used a modification (Umezu, 1995, 1999b) of the method established by Vogel et al. (1971).

On the first day, individual animals that had been deprived of water for 2 days were placed in separate chambers, and allowed free access to water for 40 min (habituation). One week later, the same animals that had again been deprived of water for 2 days before the test, underwent the Vogel conflict test 20 min after the administration of lavender oil, constituents, or vehicle. The mice had free access to water from the spout in the chamber, and the number of licks of the spout was recorded simultaneously in each chamber over 40 min. Every 20th lick was punished by an electric current (30 V, ca. 0.1 mA, 50 Hz AC, duration, 0.3 s) through the floor of the chamber, and the number of electric shocks the mice received during the 40 min was recorded.

The apparatus (Umezu, 1995, 1999a,b; Umezu et al., 2002) consisted of 5 Plexiglas chambers (180 (W)×100 (D)×120 (H) mm) and a recorder (VC-3002-L and VC-2050-L, O'hara and Co., Tokyo). A water bottle was placed on the top of each chamber, from which water was available through a spout reached from inside the chamber. The number of licks of the spout was counted simultaneously in each chamber. Every 20th lick was punished by an electric shock through the floor of the chamber.

2.5. Experimental procedures

2.5.1. Experiment 1. Effects of lavender oil in the Geller and Vogel conflict tests in ICR mice

The effects of an intraperitoneal administration of 200–1600 mg/kg of lavender oil in the Geller and the Vogel conflict tests in ICR mice were examined 20 min later.

2.5.2. Experiment 2. Identification of the constituents of lavender oil

The composition of the lavender oil tested in Experiment 1 was analyzed using automated GC/MS comprising a JMS 700 unit (JEOL) equipped with a HP5890 gas chromatograph (Hewlett-Packard) (Umezu et al., 2001, 2002). The GC was filled with a fused silica capillary column (HP-5: 0.25 mm i.d.×30 m) coated with 5% phenyl methyl silica. The column temperature was increased from 40 °C to 250 °C in 5 °C/min increments. Lavender oil and the authentic standards were diluted with n-hexane, then injected into the GC in splitless mode. The

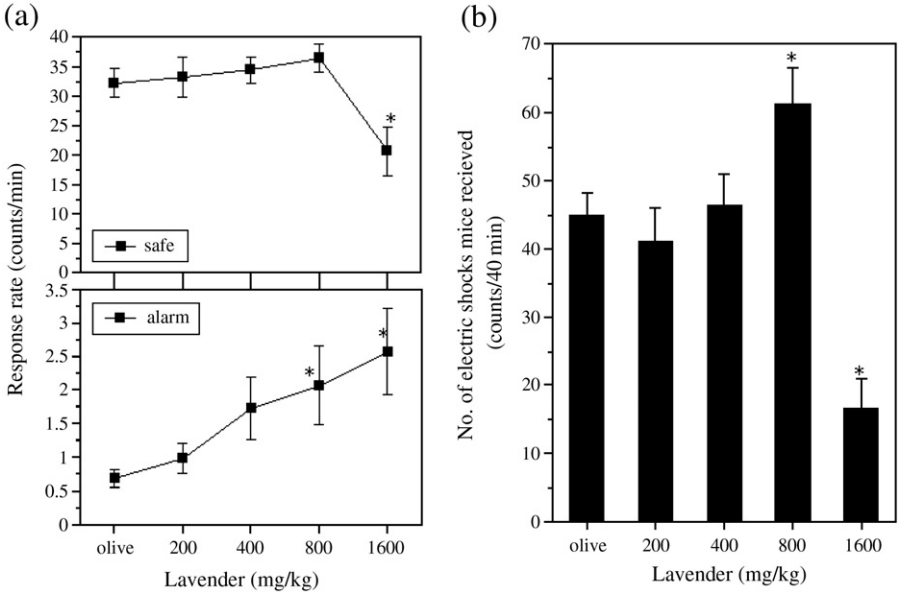

Fig. 1. Effects of lavender oil in Geller (a) and Vogel (b) conflict tests in ICR mice. Upper and lower panels of (a) show response (lever-pressing) rates during safe (unpunished) and alarm (punished) periods, respectively. Points show mean values and vertical lines show SEM. Columns in (b) show mean values of number of electric shocks mice received during 40 min of Vogel conflict test. Vertical lines indicate SEM (a, $N=15$; b, $N=30$); *, $P<0.05$.

injectior and separator temperatures were 250 °C and 260 °C, respectively. Helium was the carrier gas and the flow rate was 1.0 ml/min. Mass spectrum analysis proceeded in the electron impact ionization (EI) mode.

2.5.3. Experiment 3. Effects of constituents of lavender oil in the Geller and Vogel conflict tests in ICR mice

The effects of identified lavender oil constituents were examined using the Geller and the Vogel conflict tests in ICR

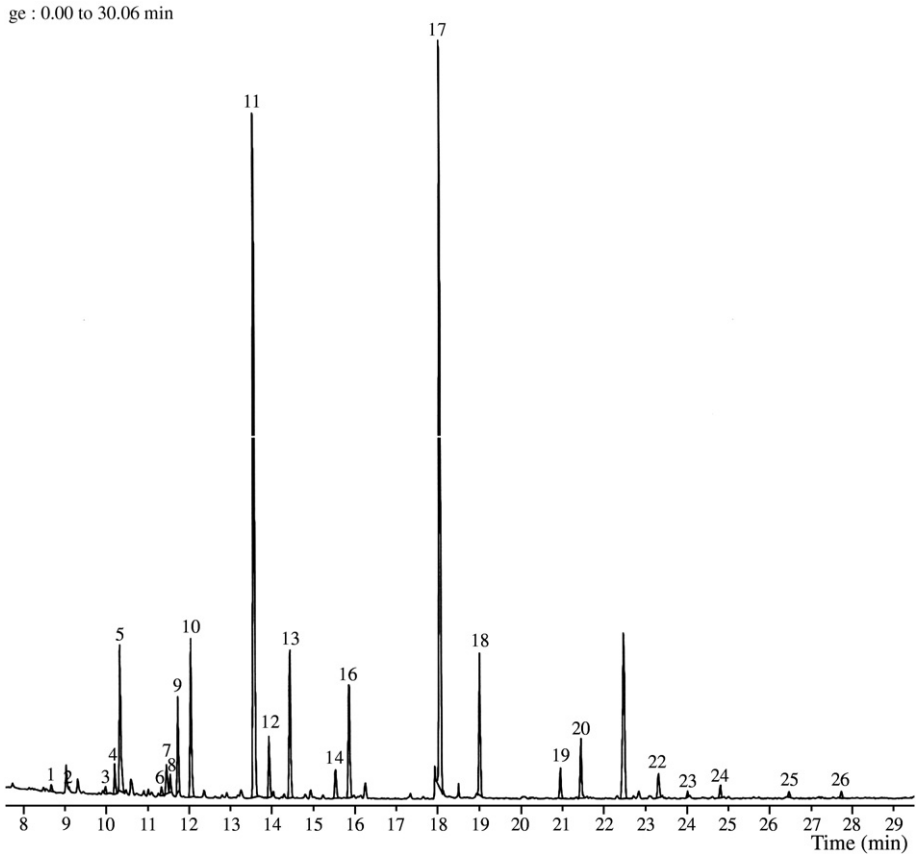

Fig. 2. Total ion gas chromatogram of lavender oil.

Table 1
Identified peaks on chromatograms (Fig. 2)

Peak No.	Retention time (min)	Area (%)	Identified compound
1	8.67	0.22	α-Pinene
2	9.11	0.06	Camphene
3	9.99	0.24	
4	10.21	0.87	
5	10.33	5.33	β-Myrcene
6	11.32	0.30	Cymene
7	11.45	1.06	Limonene
8	11.54	0.51	Cineol
9	11.73	2.66	
10	12.04	5.36	
11	13.56	26.12	Linalool
12	13.92	2.01	
13	14.44	5.78	
14	15.54	1.21	Borneol
15	–	–	
16	15.85	4.64	Terpinen-4-ol
17	18.05	26.32	Linalyl acetate
18	19.00	4.38	
19	20.96	1.11	
20	21.45	2.14	Geranyl acetate
21	22.48	7.55	Caryophyllene
22	23.32	1.03	
23	24.02	0.17	
24	24.80	0.44	
25	26.47	0.21	
26	27.73	0.28	

mice. Each compound was administered i.p. 20 min before the tests.

2.6. Statistical analyses

Overall differences in the means of all results from Experiments 1 and 3 were examined by one-way ANOVA followed by Fisher's PLSD tests. Statistical significance was established at $p<0.05$.

3. Results

3.1. Experiment 1. Effects of lavender oil in the Geller and Vogel conflict tests in mice

Lavender oil produced significant effects in the Geller conflict test in ICR mice (Fig. 1a). The response rate during the safe period significantly decreased at 1600 mg/kg ($F(4,70)=4.30$, $P<0.05$). On the other hand, the response rate during the alarm period dose-dependently increased with respect to the administration of lavender oil ($F(4,70)=2.86$, $P<0.05$). The rate significantly increased at 800–1600 mg/kg, indicating that lavender oil at these doses produced an anticonflict effect in this test. The oil also produced significant effects in the Vogel conflict test in mice ($F(4, 145)=12.71$, $P<0.05$)(Fig. 1b). The number of electric shocks the mice received increased significantly at 800 mg/kg of lavender oil, and apparently decreased at 1600 mg/kg. Thus, the oil produced a significant anticonflict effect at 800 mg/kg in this test.

3.2. Experiment 2. Identification of the constituents of lavender oil

The lavender oil tested in Experiment 1 was analyzed using GC/MS. Total ion chromatography revealed 26 significant peaks (Fig. 2). We analyzed the mass spectrum of each peak, followed by a search of the library of mass spectra of known chemicals. We then determined candidates for each constituent of lavender oil by comparing the known and observed spectra. Next, the authentic standards for each candidate were analyzed

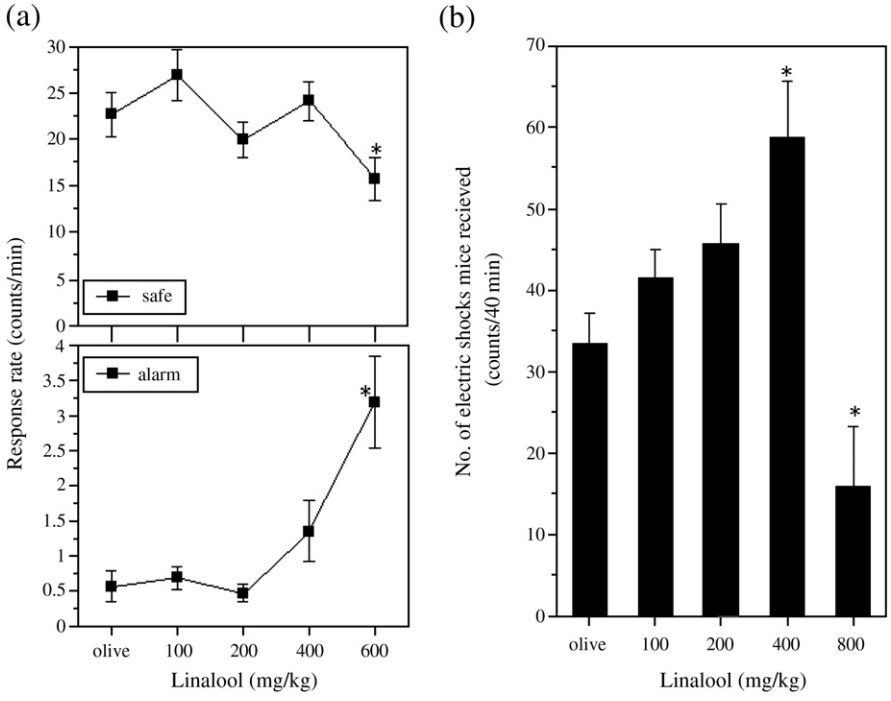

Fig. 3. Effects of linalool in Geller (a) and Vogel (b) conflict tests in ICR mice (a, $N=20$; b, $N=30$).

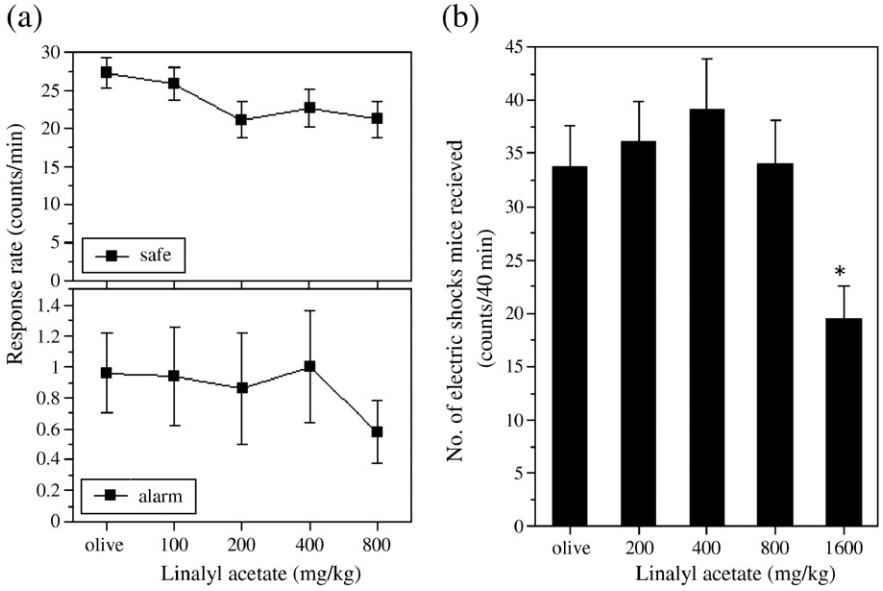

Fig. 4. Effects of linalyl acetate in Geller (a) and Vogel (b) conflict tests in ICR mice (a, $N=18$; b, $N=27$).

using GC/MS under the same conditions as in the lavender oil analysis and the results of the two analyses then compared. When the retention time on the total ion chromatogram and the mass spectrum of an authentic standard were identical to one peak in lavender oil, we concluded that the lavender oil peak was identical to the authentic standard. In this manner, we identified 12 compounds (Table 1). The remaining constituents could not be identified as authentic standards are not available for comparison. Table 1 also presents the retention time and % area on the chromatogram for each peak. According to the % area, the identified constituents accounted for about 75% of the lavender oil. In particular, linalool and linalyl acetate comprised 26.12% and 26.32%, respectively, indicating that these are the major constituents of lavender oil.

3.3. Experiment 3. Effects of constituents of lavender oil in the Geller and Vogel conflict tests in ICR mice

Fig. 3 shows the effects of linalool, a major constituent of lavender oil, in the Geller (a) and Vogel (b) conflict tests in ICR mice. Linalool significantly decreased the response rate during the safe period in the Geller test at 600 mg/kg ($F(4, 95)=3.3$, $P<0.05$), while it significantly increased the response rate during the alarm period ($F(4, 95)=9.20$, $P<0.05$). In other words, linalool produced an anticonflict effect in the Geller test. Linalool also produced a significant effect in the Vogel test ($F(4, 145)=12.71$, $P<0.05$). The number of electric shocks mice received during the 40 min significantly decreased at the highest dose of linalool (Fig. 3b). On the other hand, the

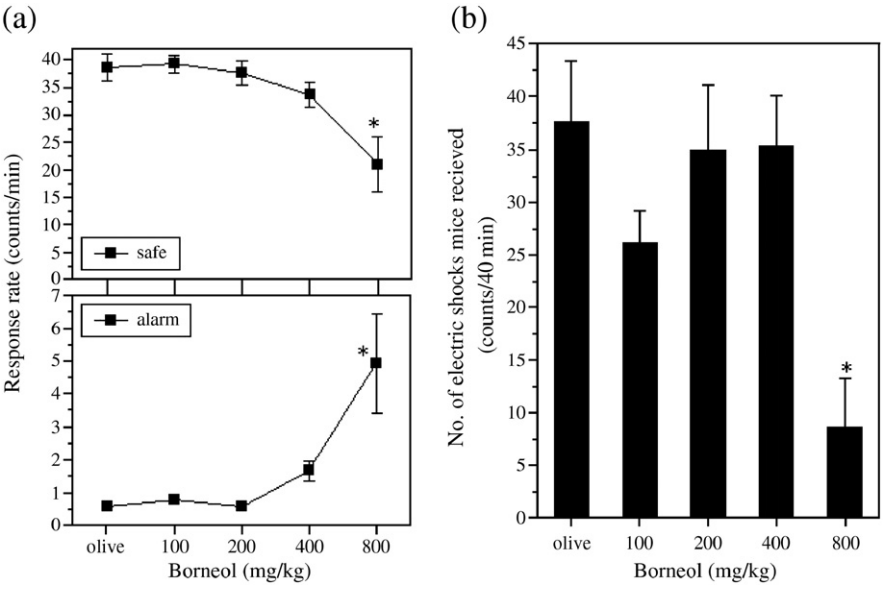

Fig. 5. Effects of borneol in Geller (a) and Vogel (b) conflict tests in ICR mice (a, $N=9$; b, $N=18$).

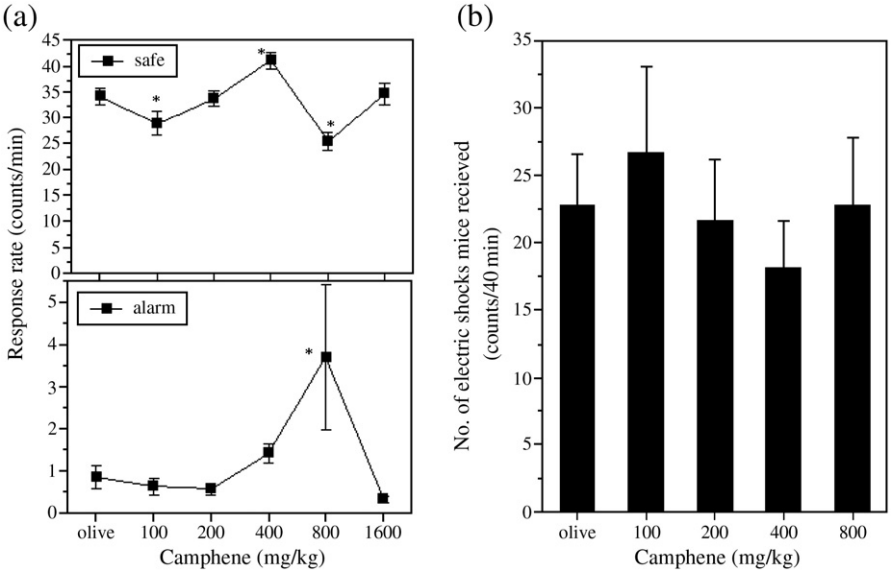

Fig. 6. Effects of camphene in Geller (a) and Vogel (b) conflict tests in ICR mice ((a) $N=9$, (b) $N=17$).

number of electric shocks the mice received increased in a dose-dependent manner at 100–400 mg/kg, indicating that linalool also produced a significant anticonflict effect in the Vogel conflict test.

In contrast to linalool, linalyl acetate, another major constituent of lavender oil, did not produce any significant anticonflict effects in either the Geller or the Vogel tests (Fig. 4). Linalyl acetate also did not produce any effect on the response rates during either the safe or the alarm period in the Geller test (safe period: $F(4, 130)=1.53$, $P>0.05$; alarm period: $F(4, 130)=0.30$, $P>0.05$). In addition, linalyl acetate did not produce any significant anticonflict effect in the Vogel conflict test, but

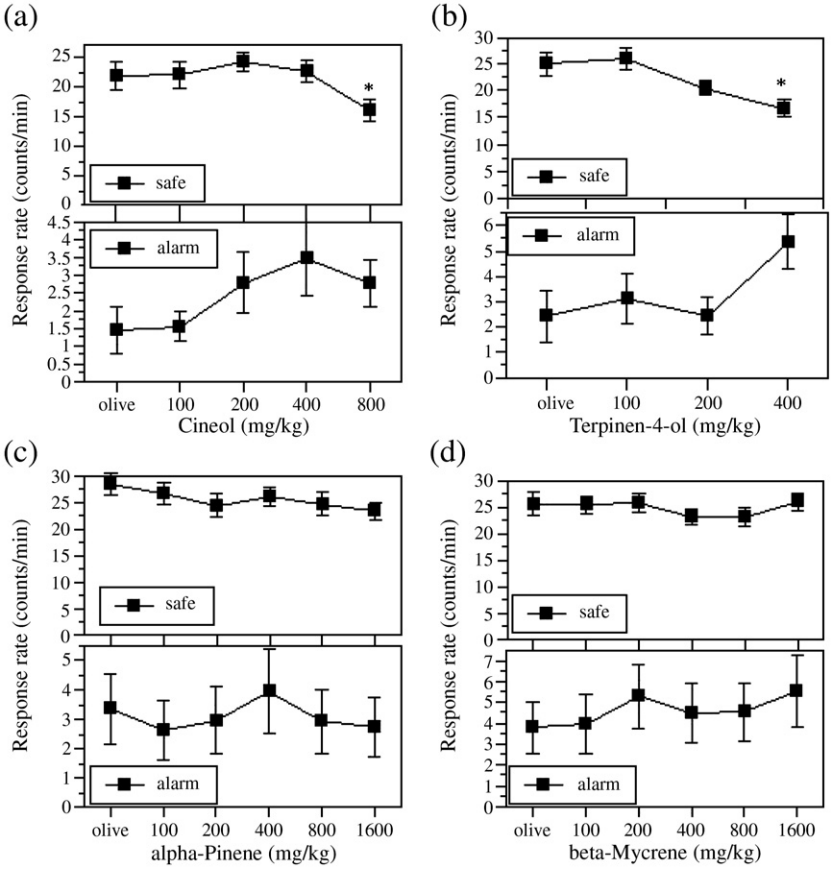

Fig. 7. Effects of cineol (a), terpinen-4-ol (b), α-pinene (c) and β-myrcene in Geller conflict test in ICR mice (a, $N=26$; b, $N=25$; c, $N=26$; d, $N=14$–15).

significantly decreased the number of electric shocks mice received at 1600 mg/kg ($F(4, 130)=3.67$, $P<0.05$).

Borneol produced a significant anticonflict effect in the Geller conflict test (Fig. 5a). The response rate during the alarm period increased significantly at 800 mg/kg ($F(4, 40)=7.12$, $P<0.05$), although the response rate during the safe period decreased significantly at the same dose ($F(4, 40)=6.67$, $P<0.05$). In contrast, borneol did not produce an anticonflict effect in the Vogel conflict test (Fig. 5b). The number of electric shocks the mice received significantly decreased at 800 mg/kg ($F(4, 85)=5.70$, $P<0.05$). Like borneol, camphene produced a significant anticonflict effect in the Geller conflict test, with the response rate during the alarm period increasing at 800 mg/kg (Fig. 6a, $F(5, 48)=2.95$, $P<0.05$). It also produced a significant effect on the response rate during the safe period ($F(5, 48)=8.68$, $P<0.05$). On the other hand, camphene did not produce any effect in the Vogel conflict test ($F(4, 80)=0.42$, $P>0.05$) (Fig. 6b).

Fig. 7 shows the effects of cineol (a), terpinen-4-ol (b), α-pinene (c) and β-myrcene (d) in the Geller conflict test in mice. Neither α-pinene nor β-myrcene produced any effects in the test (α-pinene: safe period, $F(5, 90)=1.88$, $P>0.05$; alarm period, $F(5, 90)=0.20$, $P>0.05$; β-myrcene: safe period, $F(5, 83)=1.30$, $P>0.05$; alarm period, $F(5, 83)=0.12$, $P>0.05$). Although cineol and terpinen-4-ol produced significant effects on the response rate during the safe period (cineol: $F(4, 125)=2.39$, $P=0.055$, significant by Fisher's PLSD test; terpinen-4-ol: $F(3, 56)=2.70$, $P=0.054$, significant by Fisher's PLSD test), they did not produce any significant effects on the response rate during the alarm period (cineol, $F(4, 125)=1.31$, $P>0.05$; terpinen-4-ol,: $F(3, 56)=0.95$, $P>0.05$).

4. Discussion

Lavender is a popular aromatherapy plant that has an appealing scent that has been incorporated into numerous products. In aromatherapy, lavender is believed to possess anticonvulsive, sedative and antidepressive effects, and to be useful for treating nervous breakdown, nervous tension and depression (Tisserand, 1993). The effects of footbaths with or without lavender oil on the autonomic nervous system of humans have recently been investigated (Saeki, 2000). That study found that footbaths with the oil elevated a high-frequency component (HFC) determined from power spectral analysis of heart rate variability and conferred a prolonged effect on the low-frequency–HFC ratio. This finding suggested that footbaths containing lavender oil relax humans. A study of the clinical effectiveness of essential oils among women during childbirth in the UK found that among 10 oils, lavender was the most frequently selected, suggesting that lavender relieves anxiety (Burns et al., 2000). However, as noted by the authors, to draw a firm conclusion on the effects of lavender oil on anxiety is difficult because of limitations in the methodological design of the study. Thus, the effectiveness of lavender oil for the treatment of anxiety and nervous tension remains unclear. Anticonvulsive (Yamada et al., 1994) and sedative (Buchbauer et al., 1991) effects as well as local anesthetic activity (Ghelardini et al., 1999) have been identified in animal experiments, but an anti-anxiety effect has not been demonstrated in an animal study.

Our previous study (Umezu, 2000) revealed that lavender oil produces an anticonflict effect in the Geller conflict test in mice, suggesting that the oil has anxiolytic activity. If so, then lavender oil should be useful for treating anxiety and nervous tension. Therefore, the present study first examined this notion using the Geller and Vogel conflict tests, given that anxiolytics that have been clinically applied produce significant anticonflict effects in these two tests. Lavender oil produced apparent anticonflict effects in both the Geller and Vogel tests in ICR mice in the present study. These results indicate that lavender oil possesses anti-anxiety properties. The reliability of this finding should be examined using other anxiety models such as the elevated plus maze model.

Although lavender oil clearly possesses pharmacological effects, the active constituent(s) have remained largely unknown. We previously demonstrated that the anticonflict effects of rose oil arise from the major constituents, 2-phenethyl alcohol and citronellol (Umezu et al., 2002). Thus, the anticonflict effects of lavender oil should also be derived from some of its constituent (s), given that it also contains a mixture of many chemicals that have generally been identified (Masada, 1975). However, because the precise composition of the oil used in the present study was unknown, we analyzed it using GC/MS in the same manner that we did with rose oil. The results revealed that the lavender oil we used contains α-pinene, camphene, β-myrcene, *p*-cymene, limonene, cineol, linalool, borneol, terpinen-4-ol, linalyl acetate, geranyl acetate and caryophyllene. Although 14 other peaks were observed on the gas chromatogram, they could not be identified because authentic standards are not available. These unknown constituents should be identified in a future study. However, the estimated total content of all identified compounds was over 75%, according to the % area on the chromatogram, and thus we believe that we identified the major constituents in the lavender oil used in the present study. In particular, the ratios of linalool and linalyl acetate were 26.12% and 26.32%, respectively, so these were the major constituents of this lavender oil.

We next examined the effects of these compounds using the two conflict tests in ICR mice to identify which were pharmacologically active. We discovered that linalool produced significant anticonflict effects in both tests whereas linalyl acetate did not. In addition, cineol, terpinen-4-ol, α-pinene and β-myrcene and did not elicit any significant anticonflict effects in the Geller test. These findings indicated that linalool is the major pharmacologically active compound in lavender oil.

Camphene and borneol produced significant anticonflict effects in the Geller, but not in the Vogel test. Differences in behavioral topographies might account for the difference between the two tests. That is, the Geller test elicits lever-pressing behavior driven by hunger, whereas licking behavior is driven by thirst in the Vogel test. The brain mechanisms for these two behaviors are likely different, which might account for the differences in the effects of borneol and camphene in the two conflict tests. The effects of borneol and camphene on CNS

function should be examined in future studies. One possibility is that camphene and borneol indeed participate in the anticonflict effects of lavender oil, as found in the Geller conflict test. However, the ratios of camphene and borneol in lavender oil were 0.06% and 1.21%, respectively, according to gas chromatography. Such small amounts are unlikely to produce significant behavioral effects, given that they were effective at 800 mg/kg in the Geller conflict test in the present study.

Gas chromatography showed that linalool accounted for 26.12% of the lavender oil, which elicited significant anticonflict effects in the Geller and Vogel conflict tests at 800–1600 and at 800 mg/kg, respectively in the present study. The estimated amounts of linalool in 800 and 1600 mg/kg of lavender oil are 210 and 420 mg/kg, respectively. We found here that linalool produced significant anticonflict effects in the Geller and Vogel tests at 600 and 400 mg/kg, respectively. Thus, although linalool alone could not wholly account for the anticonflict effects of lavender oil, it nevertheless could be a major source of these effects. When a mixture of many compounds is administered, interactions affecting their pharmacokinetics are likely to be complex. In addition, such complex interactions might affect the effects of such compounds on brain functions. In addition, a compound(s) that has a powerful anti-anxiety effect(s) might yet be discovered among the other unknown constituents of lavender oil. These issues need to be further examined to fully explain the anticonflict effects of lavender oil.

Little is understood about the effects of linalool on animal behavior and the brain. Linalool reduces the locomotor activity of mice, showing that it possesses a sedative effect (Buchbauer et al., 1991, 1993) as well as the acetic acid-induced writhing response and the hot plate test has shown that it also has an analgesic effect in mice (Peana et al., 2003). Opioidergic and cholinergic mechanisms might be involved in the antinociceptive effect of linalool on acetic-acid induced writhing, given that the effect of linalool is reversed by co-administration of the opioid receptor antagonist naloxone or the muscarinic receptor antagonist atropine (Peana et al., 2003).

The mechanism(s) underlying the effects of linalool on brain function remains unclear. Linalool might affect the glutamatergic system, since [$_3$H]-glutamate binding to a cerebral cortex membrane preparation is suppressed by adding linalool to the medium (Elisabetsky et al., 1995). Many studies have shown that the glutamatergic system plays an important role in the Vogel conflict behavior of rats (Millan, 2003), but the role of the system in the conflict behavior of mice is poorly understood (Umezu, 1999b; Kuribara et al., 1990). Linalool can interact with $GABA_A$ receptors *in vitro* (Hossain et al., 2002), where it potentiates the response of $GABA_A$ receptors elicited by GABA. Because $GABA_A$ receptors play an important role in the conflict behavior of rodents (Umezu, 1995, 1999a,b; Millan, 2003), this effect of linalool on $GABA_A$ receptors might be involved in the anticonflict effects of linalool. Further studies are required to clarify this notion.

Natural essential oils are suitable when the objective is to simply appreciate their scent. However, synthesized active ingredients are more appropriate for treating mental disorders. The cultivation of lavender plants is laborious and time-consuming, and lavender flowers contain only a small amount of essential oil, generally rendering the natural oil very expensive. The present study revealed that linalool is a key active constituent of lavender oil, and therefore would be a viable alternative to lavender oil for the treatment of anxiety. Because a method of linalool synthesis has been established, it can be produced in large amounts at a reasonable price. We believe that the use of linalool should be considered for treating anxiety.

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