

Effects of essential oil exposure on salivary estrogen concentration in perimenopausal women

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Abstract

OBJECTIVES: The menopausal transition is the time from the onset of menstrual changes until one year after the final menstrual period. During this phase, perimenopausal women experience a variety of health-related symptoms, which seemingly derive from declining level of estrogen secretion. It has long been recognized that some essential oils have the efficacy of alleviating menopausal symptoms. On the basis of this, it is possible that these essential oils have the potency to facilitate estrogen secretion in women. The present study investigated this possibility by examining if the olfactory exposure to the essential oil increase salivary estrogen concentration.

METHODS: We tested the effect of ten essential oils; clary sage, frankincense, geranium, lavender, jasmine absolute, neroli, rose otto, ylang ylang, orange and roman chamomile, which are thought to relieve perimenopausal symptoms.

RESULTS: The results have shown increase of salivary estrogen concentration induced by exposure to geranium and rose otto compared to control odor.

CONCLUSION: Together with the previous studies, the present study may give support to the notion that olfactory exposure to some essential oils can influence salivary concentration of estrogen.

INTRODUCTION

Menopause is the permanent cessation of menstrual cycles that generally occurs in women around 51 years of age, varying between 40 to 60 years (Treloar 1981), following the loss of ovarian follicular activity. The menopausal transition is the time from the onset of menstrual changes until one year after the final menstrual period. This transition period starts at around 47 years of age and may last for 5 to 8 years on average (Harlow *et al.* 2011). Women these days spend more than a third

of their life beyond the menopausal transition, also referred to as the climacteric years (Murphy *et al.* 2013). With the progressive aging of the population, the proportion of menopausal women is expected to increase (McKinlay *et al.* 1973). Reducing the burden imposed on perimenopausal women by menopause-related health conditions and improving overall quality of life have become increasingly important goals.

Declining and/or changing levels of estrogen are associated with the menopausal transition and may result in a variety of symptoms (Sherwin 1994;

Sherwin 2003; Schmidt 2005; Maki *et al.* 2010; Reid 2014). Most women experience these symptoms during the transition period (No authors listed. 2015). The most common symptoms include vasomotor symptoms (e.g., hot flushes and night sweats), mental symptoms (e.g., depressive and anxious moods and irritability) and urogenital symptoms (e.g., vaginal dryness) (Schindler 2006; McNamara *et al.* 2015). Of the perimenopausal women that responded to a postal survey conducted in Scotland on symptoms experienced in the previous month, 47% reported hot flushes; 46% night sweats; and 26% vaginal dryness (Duffy *et al.* 2012).

Hormone replacement therapy (HRT) is generally used to improve these symptoms during the menopausal transition, and it is considered the most effective treatment (Goolsby 2001; Sassarini *et al.* 2015). However, according to recent studies, HRT increases the risk of cancer and other diseases (Sarri *et al.* 2015; Manson *et al.* 2016; Roberts *et al.* 2016; Warren *et al.* 2015). For instance, the Women's Health Initiative (2002) and the Million Women Study (2003), reported links between combination HRT (estrogen and progestogen), cardiovascular disease and breast cancer (No author listed. 2015). Although some argue that the benefits of HRT exceed the risks for the majority of symptomatic postmenopausal women, careful cost-benefit analysis should be conducted before deciding whether to use HRT or not (Daly *et al.* 1996; Delva 1993; Canderelli *et al.* 2007).

There has been increasing interest in the efficacy of aromatherapy as a potential alternative to HRT (Jan. 2005). Large population-based research has shown that complementary and alternative medicine (CAM) constitutes a popular treatment option for perimenopausal women (Peng *et al.* 2014), partly because CAM is believed to be free from side effects. Until recently, little evidence was available regarding the efficacy of aromatherapy with the exception of anecdotes and traditional folk medicine knowledge. However, a recent questionnaire-based study has shown that aromatherapy could be an effective CAM method for perimenopausal symp-

toms in the setting of a hospital obstetrics and gynecology department (Murakami *et al.* 2005). Additionally, Fukui, Toshiyama and Komaki (2011) have revealed that exposure to saffron odor decreases salivary cortisol levels in female college students (Fukui *et al.* 2011), which supports the concept of modulatory effects of odors on endocrinological functions.

As briefly stated above, vasomotor, mental and urogenital symptoms experienced during the menopausal transition stem largely from declining levels of estrogen. Thus, if we were to identify an essential oil with the capability of increasing estrogen levels in women with perimenopausal symptoms, this could support the efficacy of CAM for perimenopausal symptoms present during the menopausal transition period. However, the effects of aromatherapy on estrogen level have not been clarified thus far. The aim of the present study was to examine the effect of essential oils on estrogen levels. We exposed to essential oils via the sense of smell in perimenopausal women and measured the salivary level of estrogen.

MATERIALS AND METHODS

Participants

Fifteen women in their late-reproductive and menopausal-transition stages participated in the experiments. One participant dropped out from the test of Jasmine absolute due to unexpected relocation. The number and the age of participants are summarized in Table 1. All participants had menstrual cycles and their period was irregular (21–37 days in length). None were habitual smokers and none reported any symptoms of postmenstrual syndrome. They participated in the present study after giving written informed consent. This study was approved by the Ethical Committee of Nagasaki University and was performed in accordance with the principles laid down in the Declarations of Helsinki.

Chemicals

The effects of 10 different essential oils were tested in the present study. The essential oils included geranium, rose otto, orange, lavender, neroli, frankincense, jasmine absolute, ylang ylang, roman chamomile, and clary sage. The ylang ylang essential oil was produced by Tree of life Co., Ltd. (Tokyo, Japan) and the others were produced by Neal's Yard Remedies (London, UK). We conducted a preliminary experiment to determine the concentration of each essential oil used in the main experiment. In this preliminary experiment, eight women (35.8±3.4 years) evaluated the pleasantness of the odors of each essential oils with varying concentrations. The participants rated the pleasantness of each odor using a 9-point Likert scale (1='I don't like at all', 9='I like very much'). In the main experiment, we adopted the maximum odor concentration to which none of the eight participants gave a rating smaller than 5 (neither pleasant nor unpleasant) in the Likert scale.

Tab. 1. Age and number of participants, who participated in the testing of each essential oil.

Essential oil	N	Age (yrs; avg ± sd)
Geranium	15	44.1±2.8
Rose otto	15	44.3±2.9
Orange	15	43.9±2.8
Lavender	15	44.4±2.6
Neroli	15	44.8±2.8
Frankincense	15	44.2±2.9
Jasmine absolute	14	44.8±2.8
Ylang Ylang	15	44.2±2.5
Roman Chamomile	15	43.9±2.4
Clary sage	15	43.8±2.5

The solvent was 98% propylene glycol or 95% dipropylene glycol. The information about the solvent, concentration, chemical composition of each essential oil is summarized in Table 2. These pieces of information were included in the brochure of the products. The chemical composition of the essential oil had been analyzed by the gas chromatography analysis. Only roman chamomile oil was separately analyzed by YAMAMOTO PERFUMERY CO., LTD. (Osaka, Japan), because the brochure of roman chamomile oil did not include necessary information.

Apparatus for Odor Exposure

The apparatus for odorant exposure consisted of an air pump, flow meter, glass bottle, silicone tube, and glass funnel. The glass bottle was filled with 15 mL of each diluted essential oil or solvent. The flow rate was set at 2.0 L/min using a flow meter. Air was first pumped into the glass bottle, and then the airflow from the bottle was delivered to the vicinity of the participant's nostrils through a silicone tube. The glass funnel served to reduce airflow stress on the participants.

Procedure

The experiments were conducted while the participants were in the follicular phase of the menstrual cycle (i.e., between days 5 and 10 after the menstrual onset). After

arriving at the laboratory, participants rested in the seated position in order to stabilize their physiological parameters. Thereafter, participants gave their saliva samples into a 1.5ml cryovial tube by passive drool.

The schedule for saliva sampling was as follows: 1) saliva collection (Control – Pre Exposure sample); 2) exposure to the scent of solvent as control for 20 min; 3) saliva collection (Control – Post Exposure sample); 4) rest for 15 min; 5) saliva collection (Essential Oil – Pre Exposure sample); 6) exposure to the essential oil for 20 min; and 7) saliva collection (Essential Oil – Post Exposure sample), as schematically shown in Figure 1). The exposure to the odor of the essential oil was always preceded by exposure to the control odor to prevent residues of the essential oil from influencing the baseline level of salivary estrogen in the control condition. After the experiment, saliva samples were stored at -80°C until use.

Analysis

Saliva samples were thawed completely and centrifuged at $1,500\times g$ for 15 min at room temperature. The estradiol concentration (17β -estradiol) in the saliva was measured using a competitive ELISA kit (High Sensitivity SALIVARY 17β -ESTRADIOL ENZYME IMMUNOASSAY KIT; Salimetrics LLC, Carlsbad, California, USA) according to the protocols recommended by the manufacturer.



Fig. 1. Schematic representation of odor exposure schedule.

Tab. 2. The composition of each essential oil used in the present study.

Essential oil	Conc. (%)	Chemical compositions (%)	Solvent
Geranium	3	citronellol (28.4), citronellyl formate (14.9), geraniol (11.0), 6,9-guaiadiene (8.3), geranyl formate (5.3)	propylene glycol
Rose otto	12	citronellol (42.4), geraniol (19.7), nonadecane (9.3), nerol (9.0)	propylene glycol
Orange	100	limonene (94.6)	dipropylene glycol
Lavender	30	linalool (42.3), linalyl acetate (34.4)	dipropylene glycol
Neroli	7.5	linalool (31.8), limonene (18.4), linalyl acetate (7.0), β -pinene (6.2)	dipropylene glycol
Frankincense	60	α -pinene (35.0), limonene (13.4), α -thujene (9.2), sabinene (5.5)	dipropylene glycol
Jasmine absolute	12	benzyl acetate (22.1), benzyl alcohol (14.1), phytol (9.2), linalool (5.1)	dipropylene glycol
Ylang ylang	1.5	germacrene D (18.5), β -caryophyllene (12.5), geranyl acetate (9.7), trans- α -farnesene (9.4), linalool (9.1), benzyl benzoate (6.5)	dipropylene glycol
Roman Chamomile	0.75	3-methyl pentyl angelate(20.7), 2-butenyl angelate(16.4), iso-amyl angelate(9.3), pinocarveol(7.5)	dipropylene glycol
Clary sage	12	linalyl acetate (68.6), β -bourbonene (10.3), germacrene D (6.9)	dipropylene glycol

RESULTS

The means, standard deviations and the confidence intervals of salivary estrogen concentration in each condition are summarized in Table 3. The salivary estrogen concentration was entered into a two-way analysis of variance (ANOVA) with the within-participant factors of Odorant (Essential Oil – Control) and Exposure Phase (Pre-Post) for the purpose of searching in an explorative manner for the essential oils that potentially facilitate estrogen secretion. We predicted that there would be a difference in the influence of odorant exposure for these essential oils compared with the control odor, resulting in a significant interaction between Odorant and Exposure Phase.

The predicted interaction between Odorant and Exposure Phase reached significance for four of the 10 essential oils evaluated: geranium [$F(1,14)=7.141$, $p=0.018$], rose otto [$F(1,14)=6.270$, $p=0.025$], jasmine absolute [$F(1,13)=6.853$, $p=0.021$], and ylang ylang [$F(1,14)=6.159$, $p=0.025$].

To clarify which essential oil affected the level of salivary estrogen, we compared the estrogen concen-

trations between pre- and post-exposure by two-tailed t -test in Essential Oil and Control Odorant conditions for the four essential oils that yielded a significant interaction. A total of eight comparisons were made. In order to control the inflation of Type I error rate, the significance level of each t -test was adjusted by Bonferroni's procedure to $p=0.00625$ ($=0.05/8$).

The analysis revealed a significant increase of the estrogen concentration during post- compared to the pre-exposure phase in the Essential Oil Odorant condition for geranium [$t(14)=3.58$, $p=0.003$], and rose otto [$t(14)=3.21$, $p=0.0062$], but not for jasmine absolute [$t(13)=2.77$, $p=0.016$], and ylang ylang [$t(14)=2.27$, $p=0.039$]. No significant results were obtained in the Control Odorant condition ($ts < 1.3$, $ps > 0.10$).

For geranium and rose otto, the increase in estrogen concentration from pre- to post-exposure phase was directly compared between the Essential Oil Odorant condition and the Control Odorant condition. The increase in the estrogen concentration was computed by subtracting the estrogen concentration in the pre-exposure phase from that in the post-exposure phase. The analyses revealed significantly larger increase of

Tab. 3. Averages and standard deviations, and 95% confidence interval of salivary 17 β -estradiol concentration in each condition.

	Control			
	Pre (pg/mL)	95% C.I.	Post (pg/mL)	95% C.I.
Geranium	2.6 \pm 0.79	[2.16, 3.04]	2.59 \pm 0.84	[2.12, 3.06]
Rose otto	2.91 \pm 0.78	[2.48, 3.34]	2.77 \pm 0.76	[2.35, 3.19]
Orange	2.45 \pm 0.67	[2.08, 2.82]	2.64 \pm 0.73	[2.24, 3.04]
Lavender	2.34 \pm 0.92	[1.83, 2.85]	2.29 \pm 0.96	[1.76, 2.82]
Neroli	2.01 \pm 0.57	[1.69, 2.33]	2.18 \pm 0.7	[1.79, 2.57]
Frankincense	3.12 \pm 0.88	[2.63, 3.61]	2.87 \pm 1	[2.32, 3.42]
Jasmine	2.33 \pm 1.29	[1.59, 3.07]	2.17 \pm 1.21	[1.47, 2.87]
Ylang Ylang	2.51 \pm 0.96	[1.98, 3.04]	2.42 \pm 0.59	[2.09, 2.75]
Roman Chamomile	2.5 \pm 0.7	[2.11, 2.89]	2.36 \pm 0.48	[2.09, 2.63]
Clary sage	2.15 \pm 0.69	[1.77, 2.53]	2.18 \pm 0.65	[1.82, 2.54]
	Essential oils			
	Pre (pg/mL)	95% C.I.	Post (pg/mL)	95% C.I.
Geranium	2.39 \pm 0.8	[1.95, 2.83]	2.64 \pm 0.89	[2.15, 3.13]
Rose otto	2.51 \pm 0.69	[2.13, 2.89]	2.89 \pm 0.78	[2.46, 3.32]
Orange	2.38 \pm 0.7	[1.99, 2.77]	2.55 \pm 0.58	[2.23, 2.87]
Lavender	2.43 \pm 1.04	[1.85, 3.01]	2.43 \pm 1.07	[1.84, 3.02]
Neroli	2.05 \pm 0.71	[1.66, 2.44]	2.07 \pm 0.68	[1.69, 2.45]
Frankincense	2.77 \pm 0.61	[2.43, 3.11]	2.74 \pm 0.92	[2.23, 3.25]
Jasmine	1.88 \pm 1.05	[1.27, 2.49]	2.24 \pm 1.21	[1.54, 2.94]
Ylang Ylang	2.1 \pm 0.59	[1.77, 2.43]	2.38 \pm 0.58	[2.06, 2.70]
Roman Chamomile	2.33 \pm 1	[1.78, 2.88]	2.51 \pm 0.5	[2.23, 2.79]
Clary sage	1.85 \pm 0.45	[1.60, 2.10]	2.05 \pm 0.55	[1.75, 2.35]

C.I.: Confidence Interval

estrogen concentration in the Essential Oil than in the Control Odorant condition for geranium [$t(14)=2.67$, $p=0.018$] and rose otto [$t(14)=2.50$, $p=0.025$].

DISCUSSION

The present study investigated the effects of exposure to essential oil odorants on the salivary estrogen levels of perimenopausal women. The essential oils tested were selected from those that have been thought to ameliorate menopause-related symptoms, such as vasomotor/urogenital symptoms and mental deterioration (Lehrner *et al.* 2000; Babar *et al.* 2015; Matsumoto *et al.* 2013; Choi *et al.* 2014; Sharifi *et al.* 2014; Lee *et al.* 2014; Maryam *et al.* 2015). In the present analyses, salivary estrogen concentration was increased by exposure to geranium and rose otto compared with the control odor.

One might find it puzzling that the averaged post-exposure concentration in the Essential Oil Odorant condition does not differ much from the average of the pre-exposure concentration in the Control Odorant condition, even for geranium and rose otto. The simple explanation for this is that the observed increase in the estrogen concentration may be a fluctuation within normal range. Thus, this possibility should be excluded more carefully in the future study in order to ascertain whether the exposure to geranium and rose otto has effects on salivary estrogen levels. One limitation of the present study is that the temporal order of the two conditions was fixed; the Control Odorant condition always preceded the Essential Oil Odorant condition. In the present study, the participants generally exhibited slight decrease in estrogen concentration after the exposure to non-odorous air in the Control Odorant condition in the tests of many odorants (7 out of 10 odorants; see, Table 3). Therefore, it is conceivable that this phasic drop in estrogen concentration during the Control Odorant condition cancelled out the numerical increase of estrogen concentration induced by the exposure to geranium and rose otto.

The previous studies have shown that detectable change in the salivary concentration of gonadal hormones can be induced within 20 min after the exposure to odorants (Fukui *et al.* 2011; Miller *et al.* 2010; Gelstein *et al.* 2011). For example, smelling saffron oil significantly increased estrogen levels in women 20 min after odor exposure (Fukui *et al.* 2011). Further, it has been reported that women's bodily odor can influence salivary testosterone level in men in 15 minutes after the exposure (Miller *et al.* 2010). Similarly, the smell of women's tear is reported to decrease salivary testosterone level in men in 15 minutes (Gelstein *et al.* 2011). Together with these studies, we believe that the present study gives further support to the notion that acute olfactory stimulation can influence salivary concentration of hormones.

What kind of mechanism underlies the link between odorant exposure and the endocrinological changes?

We tentatively speculate that the chemical components contained in both geranium and rose otto exerted biological effects. The main chemical components contained in geranium and rose otto are summarized in Table 2. Both citronellol and geraniol are the main components of geranium and rose otto. This finding indicates that the endocrinological effects induced by these odorants could be attributable to these components. Geraniol and citronellol are both monoterpenoid with similar structures (Bakkali *et al.* 2008). Thus, the resemblance in their chemical structure might explain their shared capacity to facilitate estrogen secretion in perimenopausal women. The above reasoning rests on the presumption that the chemical components, which constitute a relatively large portion of each essential oil, are responsible for the observed increase in estrogen concentration. However, it is also possible that some trace component contained in these odorants has the endocrine-modulatory potential. Likewise, it might be the combination of chemicals, rather than a single chemical component, that induced the observed effect (Araneda *et al.* 2000; Kajiya *et al.* 2001; Spehr *et al.* 2003; Katada *et al.* 2005). Therefore, it is premature to draw any conclusion regarding the mechanism responsible for the modulation of estrogen secretion.

In the present study, we did not observe any effects of the odors of the essential oils, except for geranium and rose otto. But this lack of results should be interpreted with caution; that is, this does not rule out the possibility that the other essential oils could influence the physiological function in perimenopausal women via mechanisms other than modulation of estrogen secretion (Clara *et al.* 2011), because we did not test the effect of essential oil exposure on the secretion of other gonadal hormones.

In summary, the overall results support the concept that exposure to the odors of some essential oils can potentially upregulate estrogen secretion in women during the menopausal transition. The exact nature of this phenomenon, such as the mechanism responsible for this effect, remains elusive at this point. But, together with the previous studies, the present study gives support to the notion that olfactory stimulation by some essential oils can influence salivary concentration of gonadal hormones.

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