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Review Article

How Strong is the Evidence for the Anxiolytic Efficacy of Lavender?: Systematic Review and Meta-analysis of Randomized Controlled Trials

Hyun-Ju Kang, Eun Sook Nam,* Yongmi Lee, Myoungsuk Kim

College of Nursing, Kangwon National University, Chuncheon, Republic of Korea

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SUMMARY

Purpose: Although lavender is purported to possess anxiolytic and sedative properties and is often recommended for relieving anxiety, the efficacy of lavender has not been well established. Thus, this review aimed to evaluate the anxiolytic effects of lavender aromatherapy.

Methods: Ten data bases were searched for studies published between 2000 and 2018. Randomized controlled trials investigating the anxiolytic effects of lavender aromatherapy with any type of application for persons with or without clinical anxiety were included. The outcome variables included self-rated anxiety, vital signs, and salivary cortisol and chromogranin A (CgA) levels. In the meta-analysis, standardized mean difference and 95% confidence interval were calculated as effect measures by applying the random effect model and inverse variance method.

Results: Twenty-two trials met our inclusion criteria. Lavender aromatherapy was found to have favorable effects in relieving anxiety (Hedges' $\hat{g} = -0.65$; 95% CI, −0.84 to −0.46) and decreasing systolic blood pressure ($\hat{g} = -0.22$; 95% CI, −0.43 to −0.02), heart rate ($\hat{g} = -0.53$; 95% CI, −0.74 to −0.32), and salivary cortisol ($\hat{g} = -1.29$; 95% CI, −2.23 to −0.35) and CgA ($\hat{g} = -2.29$; 95% CI, −3.24 to −1.34) levels. However, the meta-analysis did not reveal any significant effects of lavender on diastolic blood pressure (effect size: −0.17; 95% CI, −0.37–0.04).

Conclusion: Aromatherapy using lavender oil might have favorable effects on anxiety and its physiological manifestations. Future studies are recommended with an emphasis on methodological quality. In nursing practice, it is suggested that lavender aromatherapy be included in programs intended to manage anxiety in patients across diverse healthcare settings.

Introduction

Anxiety is a psychological phenomenon including apprehension, nervousness, and worry followed by physiological arousal [1]. Approximately, 4–6% of the world population is distressed with one or more anxiety disorders, manifesting symptoms such as elevated blood pressure, heart rate, and endocrinological stress markers [2].

Anxiety is a commonplace disorder but can be severe and enfeebling, often requiring pharmacologic treatment [3]. Untreated anxiety disorders might be associated with the development of co-morbidities such as depression or the emergence of harmful health behavior such as nicotine or alcohol abuse [4]. Many anxiolytics such as selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines cause side effects including amnesia, sedation, impaired concentration, or depression [5]. Therefore, there is an existing demand for effective and harmless anxiolytics [4].

Aromatherapy is the therapeutic use of essential oils from plants. Essential oils can be absorbed into the body via the skin or the olfactory system [6]. Lavender is often mentioned as the "mother" of essential oils [3]. One of the components in lavender oil, linalool, was found to have an inhibitory effect on the limbic system and autonomic neurotransmission, which ultimately lead to a drop in blood pressure [7,8], this systemic effect is associated with gamma-aminobutyric acid (GABA-A) receptors, which are known to play an important role in reducing anxiety levels [9]. Lavender oil is known to be one of the most effective essential oils for relieving anxiety disorders, and it is regarded as an accessible and safe option compared with anti-psychotic medications (e.g., alprazolam,

Hyun-Ju Kang: https://orcid.org/0000-0002-2129-1658; Eun Sook Nam: https://orcid.org/0000-0002-0785-1962; Yongmi Lee: https://orcid.org/0000-0001-7864-2669; Myoungsuk Kim: https://orcid.org/0000-0002-1495-5153

* Correspondence to: Eun Sook Nam, College of Nursing, Kangwon National University, Chuncheon, Republic of Korea.
E-mail address: esooknam@gmail.com

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lorazepam, and diazepam) [10]. Silexan, which has been licensed in 14 countries world wide and is the active substance of a medicinal product marketed in Germany, is produced from lavender and causes a potent inhibition of voltage dependent calcium channels (VOCCs) in synaptosomes, primary hippocampal neurons and stably overexpressing cell lines [11], which have been shown to play an important role in both anxiety and depression.

Accompanying the recent development of complementary and alternative medicine, scientific investigation of the effects of aromatherapy have been undertaken [12]. Many studies have demonstrated that lavender oil is associated with anxiety relief, reduction of mental stress, sedation, and good sleep [13–15] and its use in aromatherapy is one possible method for anxiolysis with few side effects [5]. Linalool and linalyl acetate which are the chemical constituents of lavender have been suggested as being responsible for reducing anxiety [16].

In addition to blood pressure and heart rate, endocrinological stress markers including cortisol and CgA are useful for objectively evaluating anxiety. Cortisol is released in response to various psychosocial stimuli via the hypothalamus-pituitary-adrenal (HPA) axis. CgA is produced by human submandibular glands and secreted into saliva. Salivary CgA has been receiving attention as a novel stress marker [12].

The anxiety relieving effect of lavender aromatherapy have been investigated across various populations, types of application, outcome measures and methodological features. Though considerable number of studies have investigated the anxiolytic effect of lavender, the findings are inconsistent across studies. Some studies reported that lavender has no significant anxiolytic effect [17–20], but many other studies showed significant anxiolytic effects [21–23]. Furthermore, the effect sizes varied across populations, intervention types, comparison conditions, and outcome measures.

There is a systematic review including 15 trials on the anxiolytic efficacy of lavender. The review summarized that lavender has favorable anxiolytic efficacy in 9 of 15 trials [3]. However, the review did not perform any meta-analysis and the overall effect of lavender for anxiety was not identified. Meanwhile, two meta-analyses investigating the effects of silexan, an orally administered lavender oil preparation, indicated that silexan has clinically meaningful anxiolytic effect [24,25]. These meta-analyses analyzed the studies without systematic reviews and silexan is only one of diverse administration methods of lavender. Therefore, the findings might not be generalized to overall lavender aromatherapy. The anxiolytic efficacy of lavender aromatherapy has not yet been well identified, thus warranting the need for a systematic review and meta-analysis on this topic.

Therefore, the present study aims to determine the efficacy of lavender aromatherapy on self-rated anxiety and its physiological referents (vital signs, salivary cortisol and CgA) using a systematic review and meta-analyses of the randomized controlled trials in people with or without medical conditions. The findings of this study can contribute to expanding the evidence on the effect of lavender aromatherapy and developing interventions to treat anxiety for patients in diverse settings of healthcare.

Methods

Criteria for inclusion

The eligibility criteria for study characteristics are as follows: (1) population: individuals of any age with or without medical conditions, (2) intervention: lavender aromatherapy with any method of application (inhalation, massage, or silexan), (3) comparator intervention: no intervention or standard/routine care or placebo, (4) outcomes: self-rated anxiety measured by validated or standardized anxiety measures (eg. Visual Analogue Scale (VAS), Spielberger State Anxiety Inventory (SSAI), and Beck Anxiety Inventory (BAI)) and physiological referents of anxiety (vital signs, salivary cortisol or chromogranin A), and (5) study design: RCTs. This study restricted the search to trials in Korean or English and published from 2000 to 2018. This study excluded trials not randomized, those that compared different types of lavender preparations without a control group, those that used combined lavender treatment, and those that investigated animal subjects.

Information sources and search strategy

The electronic databases were searched using PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, CINHAL, KoreaMed, National Digital Science Library (NDSL), KMBase, Korean studies information service system, and KISTI from March 1 to June 15, 2018. In addition, authors searched the bibliographies of the selected studies for further relevant studies. The search terms were (lavender or lavandula or silexan) and (anxiety or stress) and derivatives of these terms, including MeSH terms (see Appendix B for search terms).

Study selection

Two researchers independently evaluated study eligibility. Disagreements were resolved by consensus, which required the reviewers to discuss the reasoning for their decisions.

Data collection process and data items

This study established a coding structure and pilot-tested by entering data on seven included studies, then revised as necessary. Two of the authors independently coded the data and the other two authors verified the coded data. Disagreements were solved by communication among the authors.

The authors abstracted the descriptive or numerical data from every included study for the following: (1) characteristics of participants (such as patient population or healthy population), (2) intervention (such as method of application, dose, duration and frequency of lavender aromatherapy versus method of control or comparison treatment, i.e., no treatment, placebo treatment, usual treatment, or standard care), (3) the outcomes measured by validated or standardized measures of anxiety (e.g., SSAI, BAI, or VAS) or physiological measures of anxiety (e.g. salivary cortisol or CgA, blood pressure, heart rate), and (4) unintended adverse effects of the treatment and time of follow up.

Risk of bias in individual studies

This study assessed risk of bias according to the Cochrane Collaboration's tool for assessing the risk of bias at the outcome level [26]. Two reviewers working independently determined the adequacy of the items of the sources of bias. Each item was assessed and classified as either low, high or unclear risk of bias, and where detail was insufficient to classify the risk, this study rated it as “unclear”. Discrepancies were solved through discussion among the authors.

Summary measures and planned method of analysis

This study estimated Hedges' $\hat{g}$, which is a corrected SMD (Cohen's d) using sample size for small sample bias, and its 95% confidence interval to estimate the average effect across studies. The random effect model was used to estimate the overall effects, assuming the effects would be different depending on the health or wealth of the participants, the type, dose, or duration of lavender aromatherapy,

and study design artifacts. The authors assessed the heterogeneity of effect sizes using I^2 statistic and Cochrane's Q statistic, which has a χ^2 distribution. If an I^2 value exceeded 50% and the p-value of χ^2 was below 0.1, we concluded that there is substantial heterogeneity according to the criteria suggested in the Cochrane Handbook for Systematic Reviews of Intervention [27]. When considerable heterogeneity was observed, the authors planned to perform moderator analysis according to the method of application of lavender preparations (inhalation, massage, and silexan) and the sample size of trials to explore the sources of heterogeneity. Meta-analyses were conducted using R software package Meta version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) using the function metacont for continuous data.

Risk of bias across studies

To detect publication bias, the authors initially evaluated the symmetry of the funnel plots of standard error by effect size and then conducted Egger's regression test as test for "small sample bias". Since the statistical power of these tests is low, they should be used only when there are at least 10 studies in the meta-analysis and at least one has statistically significant results. So these tests were performed for the outcome of self-rated anxiety combining 19 studies using R software.

Results

Study selection

A total of 972 citations were retrieved by the database search. The authors identified additional eight trials meeting the inclusion criteria by examining the bibliographies of the selected articles. After excluding duplicates, 373 studies remained. Of them, 329 citations that did not meet the inclusion criteria were excluded through with examining the titles and abstracts. The full text of the remaining 44 studies were reviewed elaborately, and 22 studies not meeting the criteria were excluded. Finally, we selected 22 studies in the systematic review. No relevant unpublished citations were identified (see Figure 1). These 22 articles are listed in Appendix A.

Characteristics of included studies

Table 1 presents a summary of the 22 included studies [12,14,15,17–23,28–39]. Eight trials were conducted in Iran, two in the USA, four in Germany, and the remaining trials were conducted in Turkey, the Republic of China, Japan, the UK, or South Korea. All studies were RCTs, published in English from 2000 to 2018. Pooled rates of premature withdrawal were 1.86% and 4.20% for the lavender and control group, respectively. The included studies had a total of 2,102 participants (1,076 in the lavender and 1,026 in the control group).

In all studies, the experimental group received one of the three types of lavender preparations (inhalation, massage, or silexan) using lavender essential oil. Sixteen trials applied inhalation, four trials performed massage, and the remaining two used oral administration (silexan). The dose, time, and session of the treatment for the experimental groups are presented in Table 1. The control group received placebo, standard care, or no treatment. Efficacy of lavender on the self-rated anxiety was assessed in 19 studies. In addition, efficacy of lavender on the vital signs was assessed in six studies and the efficacy on the cortisol and CgA was evaluated in two studies.

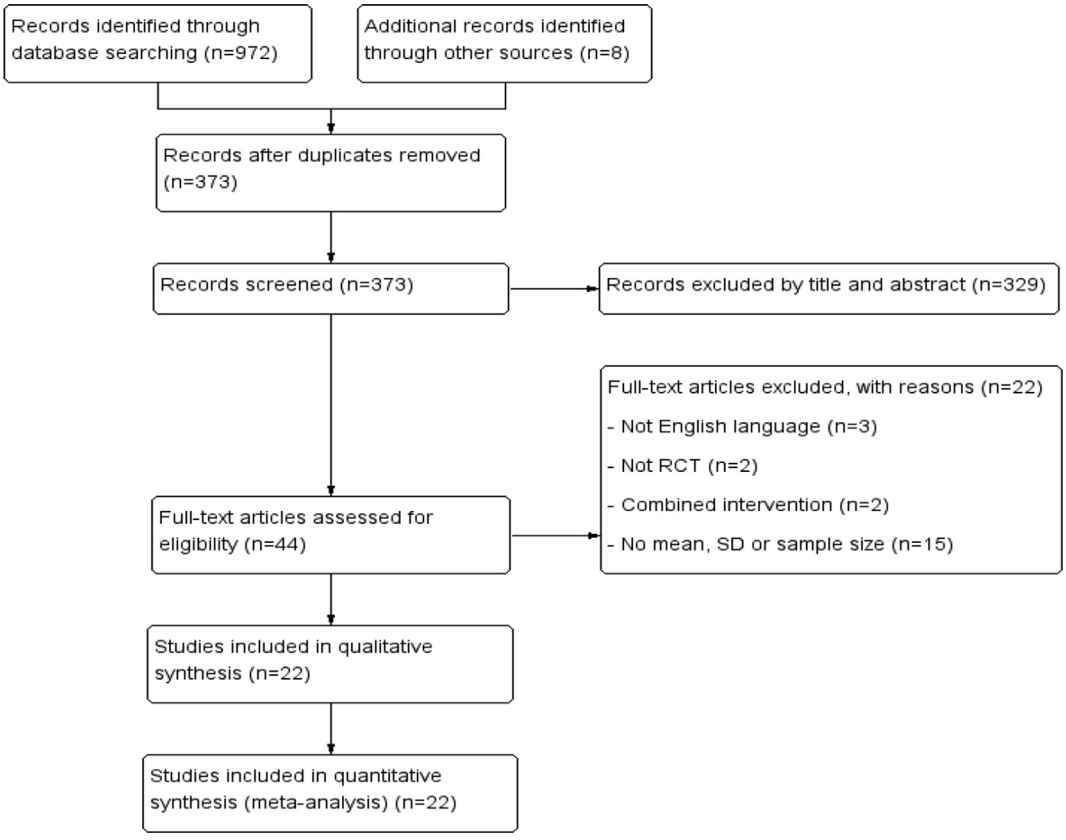

Figure 1. Flow diagram of study selection process. *Note.* RCT = randomized controlled trial; SD = standard deviation.

Table 1 *Characteristics of Included Studies on the Effect of Lavender Aromatherapy.*

First author (yr), Country	Study design	Subjects /sample size R = E:C; A = E:C	Intervention	Control treatment	Outcome measure	Session (time/session)
Yayla (2017), Turkey [17]	RCT	Patients undergoing needle insertion/ R = 41:41; A = 41:41	Inhaled 3 drops of lavender oil on a cotton swab for 3 min before needle insertion	No intervention	SSAI	1 session (3 min)
Braden (2009), USA [18]	RCT, single blind	Preoperative patients/ R = 51:49; A = 51:49	Inhaled a drop of lavandin on a cotton ball and topically placed a drop of lavandin to the pedal pulse point	Standard preoperative care	VAS anxiety	1 session (10-90 min)
Bekhradi (2016), Iran [19]	RCT	Female students/ R = 65:47; A = 61:42	Inhaled 5-6 drops of lavender oil on a cotton ball at a 5 cm distance for 5 min (once every night for a week)	No intervention	Spielberger's test anxiety scale	7 sessions (5 min)
Lee (2017), Republic of China [20]	RCT	Patients undergoing mechanical ventilation/ R = 52:52; A = 47:44	2% lavender oil massage on the back for 5 min and rest on the bed for 25 min	Had a rest for 30 min	1) STAI 2) Vital signs	1 session (5 min lavender oil massage +25 min rest)
Kasper (2010), Austria [14]	RCT, double blind	Adults suffering from anxiety/ R = 107:109; A = 104:108	Orally administered gelatine capsules containing 80 mg of silexan	Placebo capsules containing 0.08 mg of lavender oil	HAMA	70 days (1 capsule)
Kasper (2015), Austria [21]	RCT, double blind	Outpatients with a diagnosis of anxiety/ R = 86:84; A = 86:84	Silexan 80 mg	Placebo capsules containing 0.08 mg of lavender oil	HAMA	70 days (1 capsule)
Bahrami (2017), Iran [22]	RCT	Older women with acute coronary syndrome/ R = 45:45; A = 45:45	Aromatherapy foot massage with lavender oil	Routine care	1) HADS-A 2) Vital signs	1 session
Ayik (2018), Turkey [23]	RCT	Patients undergoing colorectal surgery/ R = 49:47; A = 40:40	Back massage with 5% lavender oil blended in almond oil for 10 min 2 sessions	Standard nursing care	SSAI	2 sessions (10 min)
Bakhsha (2014), Iran [28]	RCT	Patients undergoing Diagnostic Curettage/ R = 50:50; A = 50:50	Inhaled lavender oil for 60 seconds	Inhaled 0.1% lemon juice	SSAI	1 session (1 min)
Hasanzadeh (2016), Iran [29]	RCT	Patients undergoing chest tube removal/ R = 20:20; A = 20:20	Inhaled 1-2 drops of lavender oil on cotton for 20 minutes	No intervention	Spielberger situational anxiety level inventory	1 session (20 min)
Karadag (2017), Turkey [30]	RCT	Patients in coronary ICU/R = 30:30; E = 30:30	Inhaled 2drops of lavender oil on cotton gauze for 20 min before sleep (21:00-24:00)	No intervention	BAI	15 sessions (20 min)
Karaman (2016), Turkey [15]	RCT, single blind	Patients undergoing	Inhaled 2 drops of 1% lavender oil on a gauze pad for 5 min	Inhaled pure water on a gauze pad for 5 min	VAS anxiety	1 session (5 min)

		surgery/ R = 53:53; A = 51:50	before and during the peripheral venous cannulation			
Kritsidima (2010), UK [31]	RCT, single blind	Dental patients/ R = 170:170; A = 170:170	Inhalation	Inhalation (plain water)	Brief State Trait Anxiety Indicator (STAI-6)	2 sessions
Motomura (2001), Japan [32]	RCT	Healthy college students/ R = 15:14; A = 15:14	Artificial stressful condition with lavender odor	Stressful condition with no intervention	1) Stress arousal adjective Checklist (stress subscale) 2) Vital signs	1 session (20 min)
Najafi (2014), Iran [33]	RCT	Patients with myocardial infarction/ R = 33:35; A = 33:35	Inhaled 3 drops of lavender on a Kleenex for 20 min twice a day for two subsequent days	Routine care without aromatherapy	SSAI	4 sessions (20 min)
Seol (2013), Republic of Korea [34]	RCT, double blind	Patients undergoing urodynamic examination/ R = 15:15; A = 12:10	Inhalation of 5% lavender oil during urodynamic examination	Inhaled almond oil	1) Vital signs 2) Salivary cortisol	1 session (60 min)
Rajai (2016), Iran [35]	RCT	Patients undergoing coronary artery bypass graft surgery/ R = 30:30; A = 30:30	Inhalation of 2 drops of lavender oil on a cotton piece on the morning of the surgery	No intervention	1) DASS (anxiety subscale) 2) Vital signs	1 session (20 min)
Seyyed-Rasooli (2016), Iran [36]	RCT, single blind	Patients with burns/ R = 30:30; A = 30:30	Aromatherapy massage using a blend of 3 drops lavender and 15 ml almond oil for 30 min	No intervention	STAI (state anxiety subscale)	1 session (30 min)
Sgoutas-Emch (2001), USA [37]	RCT	Students undergoing arithmatic task/ R = 20:20; A = 18:12	Inhalation	No intervention	1) Spielberger state anxiety questionnaire *(6 items)* 2) Vital signs	1 session (10 min)
Toda (2008), Japan [12]	RCT	Students performing arithmetic test/ R = 16:14; A = 16:14	Inhaled airbone lavender oil	No intervention	Salivary CgA	1 session (10 min)
Uzunçakmak (2018), Turkey [38]	RCT	Students with premenstrual syndrome/ R = 45:45; A = 40:37	Steam inhalation	No intervention	Premenstrual syndrome scale (anxiety subscale)	15 sessions
Ziyaeifard (2017), Iran [39]	RCT, double blind	Patients for coronary angiography/ R = 40:40; A = 40:40	Inhaled 5 drops of lavender oil on a cotton piece for 5 min 30 min before angiography	Inhaled distilled water on a piece of cotton	Vital signs	1 session (5 min)

*Note.*A = analyzed; BAI= Beck Anxiety Inventory; CgA = chromogranin A; C = control group; CTR = chest tube removal; DASS = Depression Anxiety Stress Scale; E = experimental group; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HAMA= Hamilton Anxiety Rating Scale; min = minute; OR = operational Room; R = randomized; RCT = randomized controlled trial; SSAI= Spielberger State Anxiety Inventory; STAI= Spielberger State-trait Anxiety inventory; VAS = visual analogue scale; yr = year.

Quality assessment of included studies

Quality of each included study was evaluated for each outcome level (i.e., self-rated anxiety measures, vital signs, and cortisol and CgA). The summary of risk of bias on self-rated anxiety is presented in Figure 2. Regarding selection bias, 13 of the 19 trials performed random sequence generation adequately, but 12 of the 19 trials did not mention allocation concealment. As to performance bias, 9 of the 19 trials were rated as high or low risk on the item blinding of participants and personnel. Regarding detection bias, 13 of the 19 studies were rated as low risk on the blinding of outcome assessment. Conclusively, the overall risk of bias on self-rated anxiety could be rated as "unclear risk of bias."

A summary of the risk of bias on vital signs, cortisol and CgA is presented in Figure 3. Regarding selection bias in vital signs, two of the six trials were classified as unclear in random sequence generation, and three of the six trials were classified as unclear in allocation concealment. Regarding performance bias, two of the six studies were rated as high-risk on the blinding of participants and personnel. Regarding detection bias, two of the six trials were evaluated as high-risk on the blinding of outcome assessment. The risk of within-study bias on vital signs, if any, is unlikely to alter the results considerably and thus, can be graded as low-risk. The risk of bias on cortisol and CgA is unlikely to alter the results considerably.

Anxiolytic efficacy of lavender aromatherapy

The efficacy of lavender aromatherapy was evaluated by self-rated anxiety and physiological anxiety measures. The self-rated anxiety measures included STAI, HADS-A, BAI, HAMA, stress arousal adjective checklist, VAS anxiety, and premenstrual syndrome scale, and the physiological anxiety measures included the vital signs, salivary cortisol, and CgA levels. In case of heterogeneity in any of the pooled analysis of outcomes, a moderator analysis was performed according to the type of lavender aromatherapy application to identify the source of heterogeneity.

Effects of lavender aromatherapy on self-rated anxiety

Self-rated anxiety was measured in 19 trials, and the findings are presented in Figure 2. Lavender aromatherapy had significantly superior anxiolytic effects to control treatment in 13 trials [28,29,31–33,35,37,39]. The effects ranged from the largest

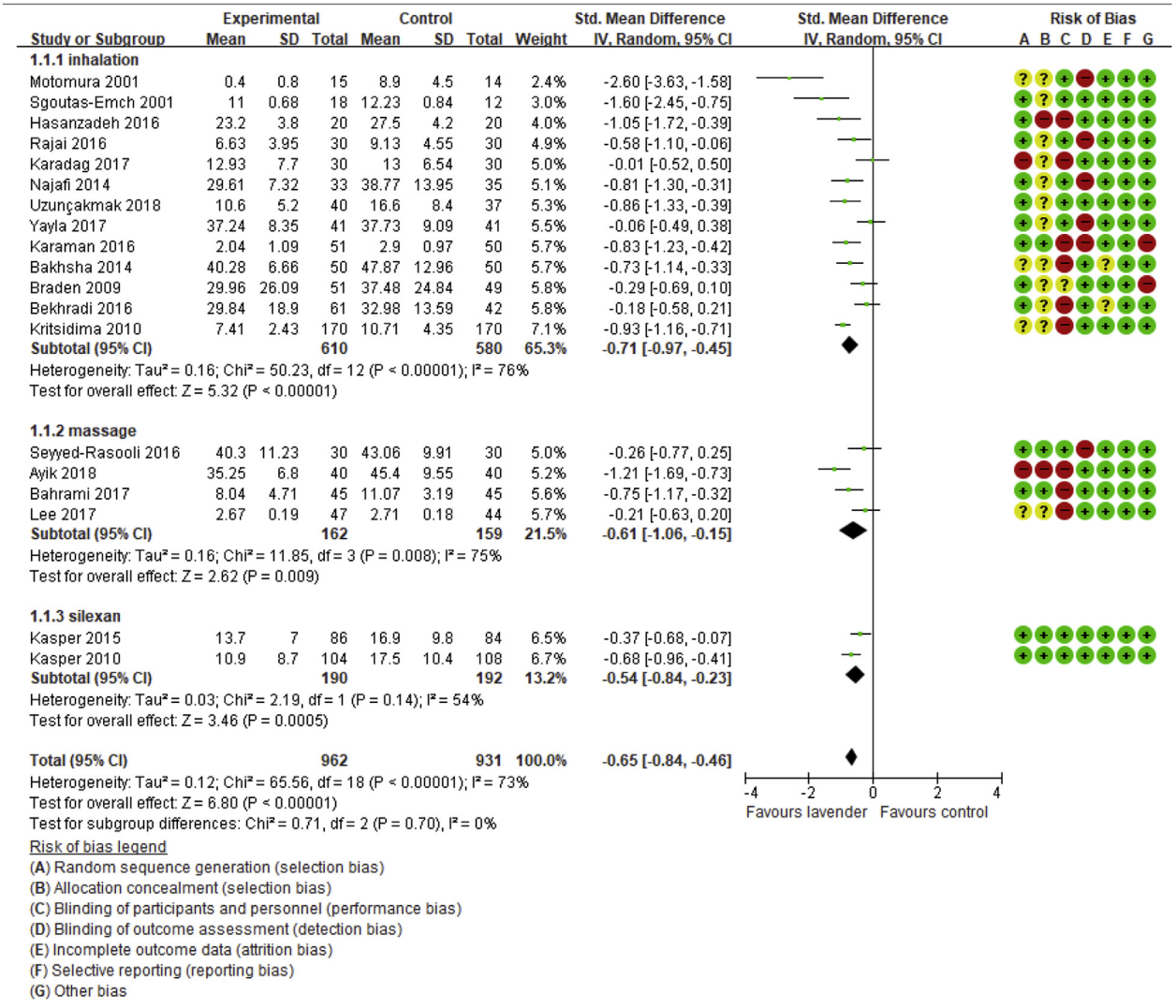

Figure 2. Meta-analysis on the self-rated anxiety with moderator analysis by methods of lavender aromatherapy and summary of assessment of risk of bias within studies.
Note. + = low risk; - = high risk; ? = unclear risk.

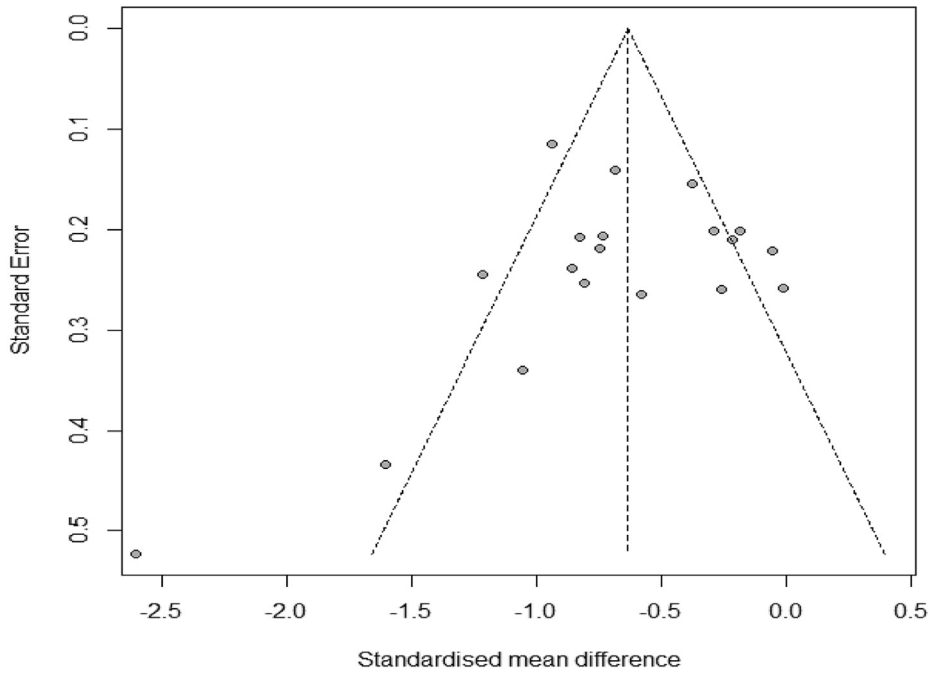

Figure 3. Funnel plot of standard error by effect size (Hedges' $\hat{g}$) for self-rated anxiety.

treatment effect of −2.6 [32] to the smallest treatment effect of −.37 [21]. The SMD (Hedges' $\hat{g}$) was −0.65 (95% CI = −0.84 to −0.46). However, the remaining six trials [30,36] showed no significant anxiolytic effect on psychological anxiety.

Substantial heterogeneity was found in combined effects ($\tau^2 = 0.12$, $\chi^2 = 65.56$, df = 18, $p < .001$, $I^2 = 73\%$). To explore possible sources of heterogeneity, this study performed moderator analyses by type of lavender intervention, healthy or illness conditions of participants, and sample size. In moderator analysis by type of lavender application, the mean effects (Hedges' $\hat{g}$) were −0.71 [95% CI (−0.97, −0.45), Z = 5.32, $p < .001$] for inhalation, −0.61 [95% CI (−1.06, −0.15), Z = 2.62, $p < .01$] for massage, and −0.54 [95% CI (−0.84, −0.23), Z = 3.46, $p < .001$] for silexan respectively; in other words, all types (inhalation, massage, and silexan) of lavender applications significantly lowered anxiety level. However, the moderator analysis using the meta-ANOVA showed no significant difference among types of lavender intervention ($\chi^2 = 0.71$, df = 2, $p = .7$). Also, the moderator analysis by healthy or illness participants showed that the mean effect ($\hat{g}$) was −1.04 [95% CI (−1.54, −0.54)] for healthy adults, −0.78 [95% CI (−1.41, −0.15)] for patients with heart diseases such as acute coronary syndrome or myocardial infarction, −0.68 [95% CI (−1.12, −0.25)] for patients undergoing invasive procedures such as chest tube removal or needle inserting and −0.72 [95% CI (−1.16, −0.28)] for patients undergoing surgery. But the moderator analysis showed no significant difference among healthy or illness groups. In summary, the average effects of lavender intervention showed differences by the methods of lavender application and health or illness groups of participants. But moderator analysis did not show significant differences.

Also, the meta-regression by sample size showed no significant moderating effect (Model Q = 0.013, d = 1, $p = .910$). This study hypothesized the types of lavender application, healthy or illness groups of participants and the sample sizes of included studies as acceptable moderators of potential variations in effect sizes across studies. In summary, the methods of application, healthy or illness groups of participants, or the sample sizes of the included trials did not significantly account for the heterogeneity across studies.

To evaluate potential publication bias, a funnel plot was drawn, then an Egger's regression test was performed for the self-rated anxiety (Figure 4). The funnel plot showed some evidence of asymmetry, being seemingly empty in the lower-right area. This means that studies with small sample and small effect are absent in the funnel. Egger's regression test was performed to assess small sample effect; however, it did not show any evidence of significant publication bias (t = −0.71, df = 17, $p = .485$).

Anxiolytic effects of lavender aromatherapy on physiologic measures

The results of the physiological measures including vital signs, salivary cortisol and CgA are presented in Figure 3. Vital signs were measured in six trials [32,34,35,39], and each meta-analysis was performed according to SBP, DBP, and heart rate. Regarding SBP, only one trial [22] showed a significant anxiolytic effect, with an effect of −0.56 (95% CI, −0.98 to −0.14), while the remaining trials showed no significant anxiolytic effect. However, the SMD (Hedges' $\hat{g}$) was −0.22 [95% CI, −0.43 to −0.02), indicating that lavender aromatherapy significantly decreased participants' SBP. There was no significant heterogeneity among the effect sizes ($\tau^2 = 0.00$, $\chi^2 = 4.60$, df = 5, $p = .47$, $I^2 = 0\%$). Regarding DBP, only one trial [22] showed a significant anxiolytic effect, and the remaining trials showed no significant effect. The mean effect was −0.17 (95% CI, −0.37 to 0.04, $p = .11$) and the treatment effects showed no inconsistency across the studies ($\tau^2 = 0.00$, $\chi^2 = 4.22$, df = 5, $p = .52$, $I^2 = 0\%$). Regarding heart rate, three trials showed significant anxiolytic effects [35,40], and the remaining trials showed no significant effects. The mean effect was −0.53 (95% CI, −0.74 to −0.32, $p < .001$), indicating that the lavender intervention significantly decreased participants' heart rate. There was no significant heterogeneity among the effect sizes ($\tau^2 = 0.00$, $\chi^2 = 3.26$, df = 5, $p = .66$, $I^2 = 0\%$).

The effects on the cortisol and CgA were estimated individually [34,38]. The findings of the two trials showed significant large effect with Hedges' $\hat{g}$ = −2.29 (95% CI, −3.24 to −1.34) for CgA and −1.29 (95% CI, −2.23 to −0.35) for cortisol, indicating that lavender aromatherapy is effective in relieving anxiety, measured by salivary cortisol and CgA.

The evaluation of publication bias was not available for vital signs, cortisol and CgA. The number of studies for tests of publication bias should be at least 10, but these outcomes were short of the number of included studies.

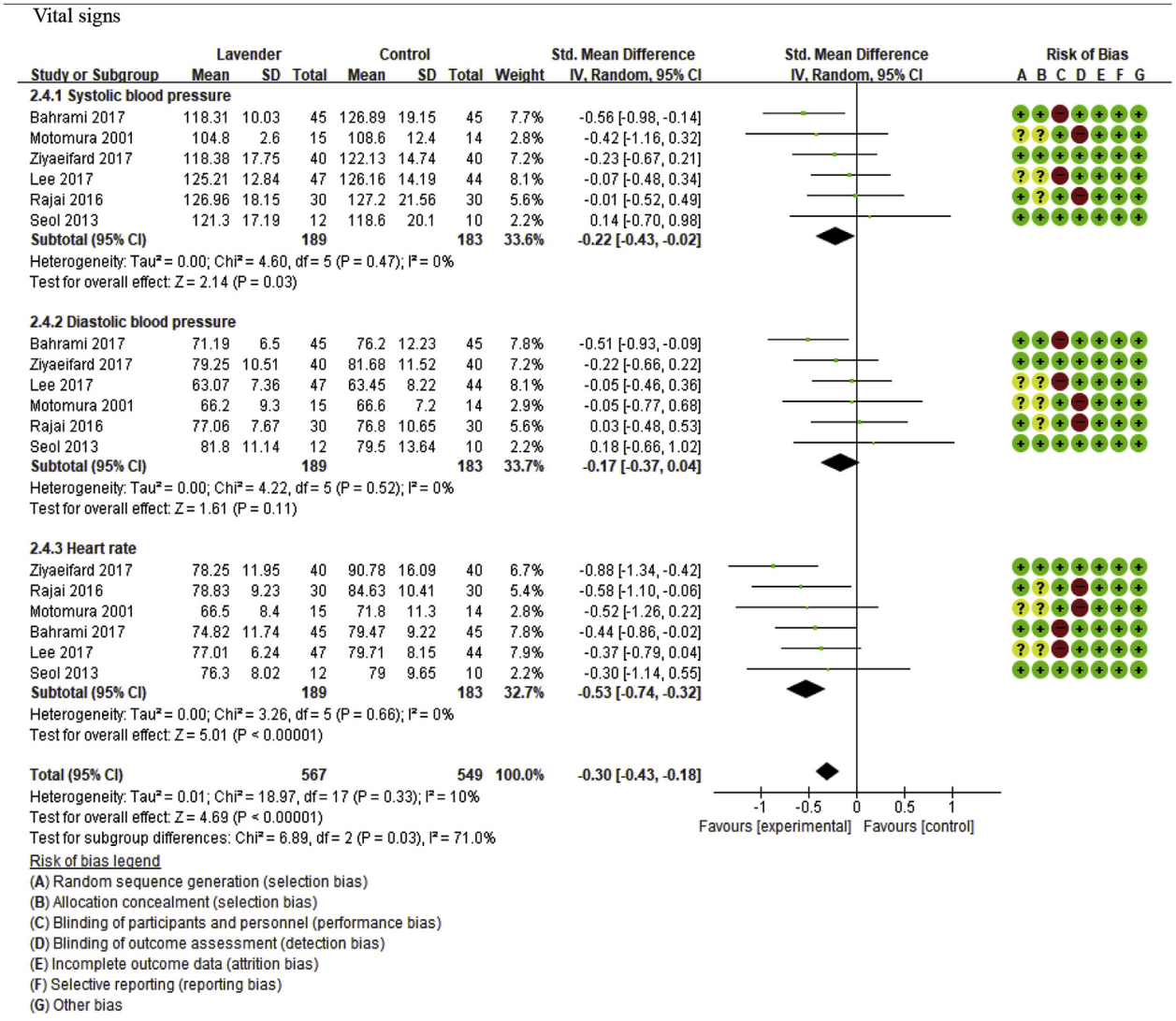

Figure 4. Meta-analyses on the physiologic measures of anxiety (vital signs, cortisol and CgA) with summary of assessment of risk of bias within studies.
Note. + = low risk; - = high risk; ? = unclear risk; CgA = Chromogranin A.

Discussion

The present study was the first systematic review and meta-analysis to investigate the anxiolytic effect of lavender aromatherapy. Our meta-analysis demonstrates that lavender is effective in reducing anxiety associated symptoms across healthy people or patients in some anxious conditions. Significant anxiety reducing effect was observed for psychic as well as for somatic manifestations of anxiety.

The mean effect size of −0.65 for *self-rated anxiety was observed in our meta-analysis.* This effect size is medium to large according to Cohen's standards [40] for interpreting SMD effect size metric. The subgroup analysis by types of application of lavender showed that the effect of inhalation was −0.71, −0.61 for massage, and −0.54 for silexan. Though the effects were different according to application type, the moderator analyses using the meta-analysis of variance and meta-regression showed no significant difference. Because the characteristic scent of lavender and massage technique, blinding of participants and personnel during the intervention might not be possible in the studies using inhalation and massage. This feature might have contributed to overestimation of the effects of inhalation and massage compared to that of silexan.

The effect size point estimate of −0.65 for overall self-rated anxiety and the result of subgroup analysis by application type, −0.71 for inhalation, −0.61 for massage, and −0.54 for silexan are not easily compared to the literature because published data on the effect sizes of lavender intervention are sparse.

Hur and colleagues published another review of 5 RCTs investigating the effects of inhalation aromatherapy on stress in healthy people. They reported a SMD of −0.96 (CI; −1.44 to −0.48) for self reported stress including 4 trials and a SMD of −0.62 (CI; −1.26 to 0.02) for cortisol combining 5 trials [6]. The effect of inhalation on self-rated anxiety −0.71 of our review is smaller than −0.96 of Hur and collegues' report. Our meta-analysis averaged 13 RCTs and the studies in Hur and collegues' review included 4 trials. Larger the sample size in meta-analysis, the smaller the standard error and then the precision of the estimation of the true effect increase. The effect of −0.71of our review on inhalation effect might be more precise because the sample size is larger.

Kim and collegues have published a review of 2 RCTs testing *massage aromatherapy* on stress in middle aged women which shows effects size of SMD, −0.64 [41]. Lee and collegues have published a review on effect of massage aromatherapy in people with anxiety. They reported a mean effect of −0.51 of self-rated

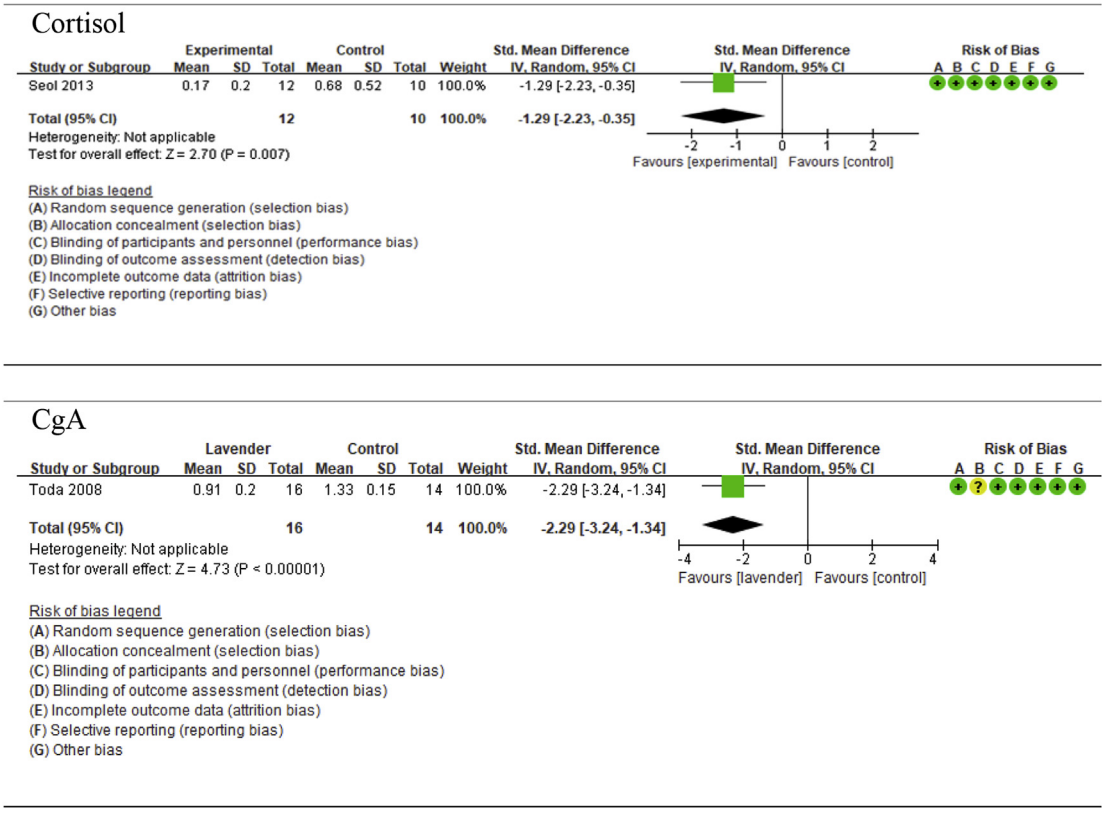

Figure 4. (*continued*).

anxiety combining 3 trials [2]. The effect size of −0.61 in our review is larger than −0.51 in Lee and collegues' review combining 3 trials, but is similar to −0.64 in Hur and collegues' review including 2 trials.

Möller and collegues have published a meta-analysis of 3 randomized placebo controlled trials on the effect of silexan for self-rated anxiety in subthreshold anxiety disorders [24]. They showed a SMD of −0.25 (CI; −0.42 to −0.08), which is small effect. The effect −0.54 of our review combining 2 RCTs is larger than Möller and collegues'. Because oral administration of silexan is permitted in a few countries, not many trials on the anxiolytic effect of silexan are searched. According to the type of application the effect size of inhalation showed the largest, and followed by massage and silexan. But as the moderator analysis showed no significant difference among the types of application, it is difficult to draw a conclusion whether the effects are different with the types of application.

The quality of evidence for the self-rated anxiety based on the risk of bias of the individual studies indicated that 9 of 19 studies in the blinding of participants and personnel, and 6 of 19 studies in blinding of outcome assessment were rated high risk of bias. Of the 3 types of lavender application, participants and personnel can be blinded to silexan completely, but applying inhalation and massage could hardly be blinded to participants and personnel. There was no evidence of publication bias by funnel plot and Egger's regression. The statistical heterogeneity of effect sizes showed substantially heterogenous. Though there was no evidence of publication bias, considering quality assessment of individual studies and substantial heterogeneity of the effects, the evidence of the effects on self-rated anxiety need to be interpreted with caution.

The meta-analyses on blood pressures and heart rate showed that the mean effect was −0.22 for SBP, −0.53 for heart rate, and −0.17 for DBP. The risk of bias of the included studies showed that 4 of 6 studies in random sequence generation was low risk, 4 of 6 studies was low risk in blinding of participants and personnel and outcome assessor, too. Because vital signs are objective, physiologic referents of anxiety, it can be considered that the internal validity for the effect of lavender on vital signs may be less moderated by blinding of participants and personnel or blinding of outcome assessment in comparison with self-rated anxiety. The heterogeneity test of the effect on vital signs was homogenous ($Q = 3.26$, $df = 5$, $p = 0.66$, $I^2 = 0\%$). The SMD of −0.22 for SBP, −0.17 for DBP, and −0.53 for heart rate observed in this review might not be compared to the literature because published data on effect of lavender on vital signs as physiological indicators of anxiety. It is recommended to include vital signs in RCTs and reviews as physiologic indicators of anxiety.

The SMD for salivary cortisol and CgA were −1.29 and −2.29 respectively, which are large effect according to Cohen's standards [40]. The effects of cortisol and CgA might not easily compared to other literature as published data are very sparse. Hur and collegues' review of 5 RCTs on the effect of inhalation of lavender in healthy people reported the effect of −0.62, but the effect estimate was not significant.

The risk of bias assessment for cortisol and CgA showed low risk in all key domains. Though the effects are considerably large and the risk of bias showed low, but the effects were estimated from only one trial for each outcome, the evidence for the effect of lavender for cortisol or CgA could not be justified to be robust. Further studies on anxiolytic efficacy of the lavender aromatherapy measuring these endocrinological referents are recommended.

This review has several limitations. First, included studies were variable in terms of participants of healthy or disease relating, types of intervention, and methodological qualities across studies. So, this study used random effect model for combining the effects of these trials and performed subgroup and moderator analysis or meta-

regression for exploring the possible sources of heterogeneity across studies. Future reviews is recommended considering these diverse features in designing the inclusion criteria of trials. Second, RCTs reporting vital signs, cortisol or CgA as physiological referents of anxiety are very limited and sample sizes for meta-analysis for physiological outcomes was small. Therefore, the generalizability of the findings of this meta-analysis may be limited, and the findings must be interpreted with caution. Future trials measuring physiological referent of anxiety such as vital signs, cortisol or CgA are recommended.

Conclusions

This meta-analysis showed that the anxiolytic effect of aromatherapy using a single lavender essential oil was evident in both self-reported anxiety and physiological manifestations of anxiety such as blood pressures, heart rate, cortisol or CgA. None of the reviewed articles reported adverse effects. Thus, the beneficial, anxiolytic effect of lavender aromatherapy was observed for both mental and physical aspects of anxiety, and lavender aromatherapy might be a generally safe anxiolytic intervention. In nursing practice, it is suggested that lavender aromatherapy be included in programs designed to alleviate anxiety in patients across diverse healthcare settings.

Declaration of competing interest

No potential or any existing conflict of interest relevant to this article was reported.

Appendix A & B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anr.2019.11.003.

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