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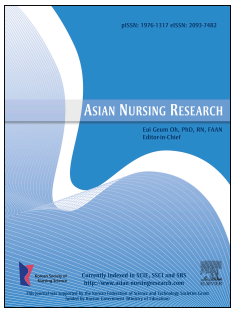

Effects of lavender on anxiety, depression and physiologic parameters: Systematic Review and Meta-Analysis

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Title

Effects of lavender on anxiety, depression and physiologic parameters : Systematic Review and Meta-Analysis

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Conflict of interest

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

Running head

Effects of lavender on anxiety, depression and physiologic parameters : Systematic Review and Meta-Analysis

ABSTRACT

Purpose: The recent evidence suggested substantial anxiolytic efficacy of lavender. The aim of this study is to examine the efficacy of lavender for anxiety, depression and physiological parameters and to elucidate the differential effects of lavender on anxiety and depression by study characteristics. *Methods*: A systematic review and meta-analysis was performed following the PRISMA guidelines. We searched PubMed, Embase, Cochrane Library, Web of Science, and Cumulative Index of Nursing and Allied Health Literature databases for randomized controlled trials investigating the efficacy of lavender on anxiety, depression or physiologic parameters in humans. We assessed risk of bias within studies with the revised Cochrane risk of bias tool for randomized trials. We used random effect model to estimate the average effect and computed bias corrected standardized mean difference as effect size metric, Hedges' ĝ for all outcomes. *Results*: Lavender was superior to placebo or no treatment in reducing anxiety (Hedges' ĝ= -0.72, 95% CI; -0.90 to -0.55, p-value<.001), depression (Hedges' ĝ= -0.43, 95% CI; -0.59 to -0.27, p-value<.001) and systolic blood pressure (Hedges' ĝ=-0.23, 95% CI; -0.41to -0.05, p-value=.01). The moderator analysis by meta-regression indicated that route of administration accounted 6.5% (p-value=.187) for the heterogeneity in anxiolytic effects, sessions of treatment accounted 13.2% (p-value=.055), and participants' health state accounted 8.9% (p-value=.131) for the variance in anxiolytic effects. *Conclusions*: Lavender aromatherapy showed substantial effect in reducing anxiety and depression, and sessions of administration increased the anxiolytic effects. The effects on physiological parameters showed small with inconsistent significances and randomized controlled trials on effect of lavender on depression were scarce. Future trials on depression and physiologic parameters are recommended and increasing the sessions of administration is recommended.

Keywords: lavandula; anxiety; depression; systematic review; meta-analysis

Introduction

Anxiety disorders are the most prevalent mental disorders around the world and are associated with significant comorbidity and morbidity [1]. Anxiety is a characteristic feature of modern times, and the prevalence of anxiety disorders has increased in response to political, societal, economical, and environmental changes [2]. The result of meta-regression adjusted for methodological difference indicated the global prevalence of anxiety disorders as 7.3% [3].

The etiology of anxiety disorders includes an interaction of psychosocial factors, e.g., childhood adversity, stress, or trauma, and a genetic vulnerability, which manifests in neurobiological and neuropsychological dysfunctions [4]. Anxiety disorders are often comorbid with other anxiety disorders, major depression, or substance abuse [5]. Current anxiolytic treatment options have limited efficacy, such as delayed onset (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, buspirone) as well as potential for habituation, tolerance, and abuse (e.g., benzodiazepines, pregabalin) [6]. In addition, anxiolytic agents may cause side effects such as sedation, impaired concentration, amnesia, depression, delirium, dependency, and, not least, withdrawal syndrome [7]. Therefore, there is a demand for efficacious, safe, and acceptable anxiolytics that are also applicable in subthreshold conditions [8].

Lavender oil administered by different routes has been recognized for centuries for promoting “well-being” and for reduction of distress [9]. Lavender, a plant from the Lamiaceae family, comes in many species with different chemical characteristics. The lavandula genus

has approximately 30 species grown around the world that share similar major chemical constituents and properties [10]. Lavender oil is the essential oil extracted from flowers and stalks of the lavender plant by steam distillation. It is a colorless or pale-yellow liquid with a sweet, floral, herbaceous aroma [11]. Lavender oil is a multi-ingredient mixture that contains more than 160 substances. The major components of lavender oil are linalool, linalyl acetate, 1,8-cineole, b-ocimene, terpinen-4-ol and camphor [12].

Silexan, a proprietary essential oil from *Lavandula angustifolia* flowers, has been approved in Germany and several other countries for the oral treatment of anxiety [9]. Silexan® showed pronounced anxiolytic effects in patients with subthreshold anxiety disorders [13-14] at a daily oral dose of 80 mg (1 capsule) as well as in anxiety related restlessness and agitation [15] and Generalized Anxiety disorder (GAD) for daily single doses of 80 mg and 160 mg [16-18]. Moreover, evidence for antidepressant-like properties of Silexan® have been observed in anxious patients suffering from comorbid depressive symptoms and in patients with mixed anxiety-depression disorder [19] which may indicate intrinsic antidepressant-like properties independent of its anxiolytic activity [20].

The neuroendocrine response to the stressors involves the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, resulting in the release of the glucocorticoid hormone cortisol from the adrenal cortex into blood, and the autonomic response is the activation of the sympathetic-adrenergic system, culminating in the release of adrenaline and noradrenaline from adrenal medulla into the blood circulation [21]. Cortisol is produced in the adrenal cortex, and is the main glucocorticoid hormone in humans. It is released in response to various psychosocial stimuli such as anxiety, stress via hypothalamus-pituitary-adrenal (HPA) axis. Endocrinological stress markers such as cortisol are useful for objectively evaluating psychosocial distress including stress or anxiety. In addition to self-reporting anxiety measure,

physiological parameters including blood pressures, heart rate or salivary cortisol level are useful for evaluating anxiety objectively.

The existing evidence have suggested anxiolytic and anti-depressant properties of lavender based on clinical trials. However, the evidence based on systematic review and meta-analysis have concentrated on anxiolytic effects exclusively [22-24]. And the reviews have presented the overall anxiolytic effects with substantial heterogeneity, but the potent source of variations in effects, such as study design, sample characteristics or intervention characteristics have not yet identified adequately.

The first aim of current review is to identify the overall effects of lavender for anxiety and its physiological referents and depression. The second aim is to investigate moderating factors for substantial variations in effect on anxiety and depression. Specifically we assumed that the effects of lavender might vary with the study characteristics comprising the routes of administration, sessions of intervention, and health conditions of populations. The results of this review could provide a scientific evidence for applying lavender for amelioration of anxiety and depression levels.

Methods

Study design

A systematic review and meta-analysis was performed to examine the effects of lavender on anxiety, depression and physiologic parameters following the PRISMA guidelines.

Eligibility criteria

Study characteristics used as criteria for eligibility are as follows; (1) population: clinical trials with human subjects of any age, sex, with or without diseases were included; (2) intervention: lavender administration with any route of administration, any type of preparation and any species of lavender (3) comparator: no intervention, standard or routine care, or placebo; (4) outcomes: primary outcomes were anxiety and depression measured by validated or standardized measures, secondary outcomes were physiological parameters of anxiety, ie, blood pressures, heart rate, or salivary cortisol and (5) study design: randomized controlled trials (RCTs). We excluded randomized clinical trial studies that compared different types of lavender preparations without a control group or used combined lavender treatments. Trials with missing essential data were excluded from qualitative and quantitative synthesis. Trials with animal subjects were excluded.

Report characteristics used as eligibility criteria are all studies written in English and published from 2010 to 2019. Since recent systematic reviews and meta-analyses on assessing the effect of lavender in the treatment of anxiety screened up to November 2018 [22-24], we limited publication year from 2010 to 2019 for up-to-date evidence and avoiding duplication of results. Trials regardless of publication status were all included except for those published in abstract form only.

Information sources

The title/abstract/key words fields of Cochrane Library, Medline and PubMed Central (PMC) via PubMed, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and Web of Science data bases were systematically searched for eligible articles.

We checked out references of articles retrieved from data base searches to locate additional relevant articles.

Search

We searched data bases and references from located articles from May 15, 2019 to June 15, 2019. We used Boolean operators to search for the following terms: (*lavender OR lavandula OR silexan)* AND (*anxiety OR anxious OR anxiolytic OR stress* OR *depression OR depressive)* and derivatives of those terms, including MeSH thesaurus terms. We set additional filters to publication years : 'from 2010 to 2019', article type : 'randomized controlled trial', language : 'English', and species :'humans' in the data base searches. The full electronic search strategy for Medline and PMC was presented in supplementary material (Appendix E).

Study selection and data collection process

Two reviewers (E.N. and Y.L.) performed eligibility assessment individually. In case of disagreement the items were discussed and resolved by consensus between the two reviewers. We then established a coding structure for data extraction and pilot-coded it on five randomly selected included trials and revised it accordingly. Two of the authors (M.K. and H.K.) independently coded the data and the other two authors (E.N. and Y.L.) checked the coded data. Disagreements were resolved through discussion among all reviewers.

Data items

The authors extracted the following descriptive and numerical data from the included studies: (1) settings, characteristics of participants; (2) intervention (such as a method of application, dose, frequency and duration of lavender aromatherapy); (3) measured outcomes of anxiety, depression and physiological parameters of anxiety; (4) comparator interventions (5) adverse effects of the intervention (6) numerical data for meta-analysis: mean, standard deviation, randomized and analyzed sample sizes of treatment groups, sessions and doses of interventions, length of follow up.

Risk of bias in individual studies

Bias assessment was performed by two independent assessors (M.K. and H.K.) based on the primary outcome (self-rated anxiety and depression) level using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [25]. Disagreements were resolved by discussion between reviewers (E.N. and Y.L.) until consensus was made. As we planned to estimate the effect of starting and adhering to lavender intervention, we assessed risk of bias based on per-protocol analysis.

The RoB 2.0 for individually randomized trials has five domains, including bias (1) from the randomization process, (2) due to deviations from intended interventions, (3) from missing outcome data, (4) in measurement of the outcome, and (5) in selection of the reported result. Each risk of bias domain has three response options comprising low, some concerns and high risk of bias. One of the key innovations of the RoB 2.0 is automatic judgement of overall risk of bias via algorithm by the risk of bias judgements of the individual domains in each study.

Summary measures and synthesis of results

In the meta-analysis of all outcomes including anxiety, depression, and physiological parameters, the bias corrected standardized mean difference (Hedges' ĝ) was calculated as the effect size metric. Standardized mean differences are upwardly biased when samples are small, especially less than 20 participants, and Hedges suggested a correction for small sample bias, known as Hedges' ĝ [26].

We assessed the heterogeneity in effects using I^2 statistics and Cochran's Q based on Chi^2 statistics. If an I^2 value was greater than 50% and the p-value of Chi^2 was below 0.1, we concluded that there was substantial heterogeneity.

We used the inverse variance weighting for pooling the results of individual studies. Based on the assumption that the true effect might vary across samples and populations, depending on health conditions of populations, type or sessions of interventions and study design artifacts, we estimated the mean effects using the random effect model.

Meta-analyses were calculated in R software Version 4.0.2 [27] using packages meta and metafor. We also performed meta-analyses in Review Manager 5.4 (Version: 5.4.1) [28] using Non-Cochrane mode.

Risk of bias across studies

Publication bias across studies was assessed with funnel plot followed by linear regression of intervention effect estimate against its standard error (Egger's regression) as tests for funnel plot asymmetry. Publication bias was assessed only when at least 10 studies were included in the meta-analysis because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry [29]. We assessed publication bias in each meta-analysis on the primary outcomes anxiety and depression respectively.

Additional analyses

When substantial heterogeneity in effects in any meta-analysis were identified, moderator analysis by meta-analysis of variance (ANOVA) and/or meta-regression was performed in order to examine factors creating variations in effect sizes across studies.

In each meta-analysis, subgroup analysis and/or moderator analysis was performed to see whether lavender intervention might have differential effects for different subgroups by study characteristics. Moderator analysis can be performed by two main statistical methods including meta-ANOVA and meta-regression, both approaches require at least 10 studies for every moderator in the analysis. In the meta-analysis on anxiety, we performed three moderator analyses by the route of administration, health state of participants and sessions of treatment. Meta-regression was used to identify the amount of heterogeneity accounted for by each moderator respectively.

In the meta-analysis on depression, as the number of included studies was ten, we performed a moderator analysis by the route of administration of lavender.

To identify the effect of risk of bias assessments for the variation of mean effect, we performed a sensitivity analysis to examine whether inclusion of the studies at high overall bias influences the mean effect. And we performed a subgroup analysis by assessment of risk to examine the difference between studies at high, some concerns, and low risk.

Results

Study selection

A total of 562 citations were retrieved through database searches and additional 12 trials were identified by reviewing the references of the selected articles. After duplicates were excluded, 378 studies remained. Then we evaluated the titles and abstracts and excluded 298 articles. The remaining 80 full text articles were screened for eligibility and 42 articles were excluded. Finally 38 articles were included in qualitative analysis and 37 articles were included quantitative synthesis. Details of the process of screening and selection of the studies were presented in Figure 1. The final included articles are listed in the supplementary material (Appendix A).

Study characteristics

Characteristics of all included studies were summarized in the supplementary materials (Appendix B). Methods and overview of the studies are as follows; 38 randomized controlled trials published in English from 2010 to 2019 were included in qualitative synthesis, and 37 of 38 studies were included in quantitative synthesis. Geographic origins of the studies are Iran (17 trials), Turkey (8), Germany (4), Greece (1), India (1), South Korea (2), Taiwan (3), USA (1) and Thailand (1).

Across all studies included in quantitative analyses a total of 4316 participants were randomized to either lavender (2165) or control treatment (2151). In the meta-analysis on anxiety a total of 3906 participants (lavender 1955, control 1951) were randomized and 3825 (lavender 1917, control 1908) were analyzed. In depression, a total of 1312 participants (lavender 657, control 655) were randomized and 1282 (lavender 644 and control 638) participants were analyzed. Studies included in meta-analysis on cortisol a total of 206

participants were randomized to either lavender (102) or control treatment (104) and 180 (lavender 96, control 94) were analyzed. Pooled premature withdrawal rates were 1.94% for lavender and 2.2% for control group in analysis for anxiety, 1.98% for lavender and 2.60% for control group in analysis for depression and 5.9% for lavender and 9.6% for control in analysis for salivary or serum cortisol respectively.

The populations of the studies included in analysis for anxiety consisted of patients undergoing surgery or invasive procedure, critically ill patients with cardiac diseases or in intensive care units, healthy students under stressful conditions, pregnant or postpartum women, and patients in anxiety and/or depressive disorders. The participants of studies on depression were composed of patients undergoing hemodialysis, women in pregnancy, postpartum, or menopause, patients in anxiety and/or depression or dementia, or healthy students with premenstrual syndrome.

The participants in experimental group received one of four routes of administration of lavender; inhalation, massage, tea or oral preparation (silexan). The participants in control group received standard or routine care, placebo, or no treatment. The details of dose, duration, and sessions of experimental and control treatments are presented in supplementary material (Appendix B).

The primary outcomes measured were anxiety and depression and the secondary outcomes measured were physiological indicators of anxiety. Of all 38 included studies, self-rated anxiety was assessed in 30 studies, depression was evaluated in 10 studies. Anxiety was measured by standardized measure (visual analogue scale) or validated measures (Beck Anxiety Inventory, Depression Anxiety Stress Scale, Hospital Anxiety and Depression Scale, Hamilton Anxiety Scale, Modified Dental Anxiety Scale, State Trait Anxiety Inventory or Zung self-rating scale). Depression was measured by validated measures including Beck

Depression Inventory, Cornell Scale for Depression in Dementia–Chinese version, Edinburgh Postnatal Depression Scale, Premenstrual syndrome (depressive affect subscale), Hospital Anxiety and Depression Scale, Hamilton Rating Scale for Depression, and Montgomery Åsberg Depression Rating Scale.

Blood pressures were assessed in 7 studies and heart rate was assessed in 6 studies, salivary cortisol was assessed in 2, and serum cortisol was assessed in 1study.

Risk of bias within studies

Figure 2A. shows risk of bias summary presenting the assessment in each domain and overall risk of bias. The overall risk of bias was evaluated as low in 16 trials, as some concern in 16 trials and as high risk of bias in 5 trials.

The risk of bias from the randomization process was rated as high in only one study, some concern in 10 studies and low in the remaining 26 studies. Bias in measurement of the outcome was assessed as high in 4 trials, some concern in 15, and low in 18 trials. Bias due to deviations from intended interventions was rated as some concern risk in only two trial and low risk in the remaining 35 trials. Figure 2B. presents risk of bias graph of included studies according to the revised Cochrane risk-of-bias tool for randomized trials (ROB 2).

Results of individual studies and synthesis of results

We first conducted basic meta-analyses for each outcomes: anxiety levels, physiological parameters (systolic blood pressure, diastolic blood pressure, heart rate, cortisol levels), and depression levels respectively.

As treatment effects are inconsistent across study characteristics of populations, sessions, durations, and types of intervention, comparison conditions, and methodological features, we hypothesized that the route of administration, sessions of treatment and health state of population might moderate variations in effect sizes across studies. Subgroup and moderator analysis may be used to explore possible sources of variability in combined effects. According to *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 [29], subgroup and moderator analysis require at least 10 studies for each moderator. The reason is the statistical power of moderator analysis is affected by number of included studies and moderators. As our meta-analysis on anxiety included 30 studies, we conducted 3 subgroup and moderator analyses by route of administration, health state of population and sessions of treatment using meta-analysis of variance or meta-regression whether the moderator variable is continuous or categorical. Also, the analysis on depression included 10 studies, only one moderator analysis by the route of administration was conducted.

Finally we performed sensitivity analysis to determine the effect of study quality on the mean effect. Specifically to examine the inclusion of studies at high risk of bias affect the overall effect on anxiety levels, sensitivity analysis deleting each study was done.

The meta-analysis for self-rated anxiety included 30 studies to evaluate the overall effects of lavender intervention (Figure 3A). Lavender was significantly superior to comparators (standard care, placebo or no treatment). The mean effect (Hedges' $\hat{g}$) was -0.72 (95% CI -0.90 to -0.55) and the direction of the mean effect favored lavender. The analysis also showed that lavender intervention was significantly superior to comparator in 21 out of 30 trials, with the

largest effect of -2.56 (95% CI -3.25 to -1.86). The heterogeneity statistics were I^2=84%, p>0.001, indicating substantial heterogeneity.

The results for the physiological parameters are presented in Figure 3B. The efficacy on the self-rated anxiety were not supported by the physiological parameters except for systemic blood pressure (SBP). Each meta-analysis for SBP and DBP included 7 studies, and 6 studies for heart rate, and 3 studies were included in the analysis for cortisol. The effect size on the SBP was -0.23 (95% CI -0.41 to -0.05). The effect of lavender on diastolic blood pressure was -0.15, the effect on heart rate was -0.2, and the effect on salivary/serum cortisol was -1.4, respectively. However, the effects of diastolic blood pressure, heart rate and cortisol showed no significance.

The meta-analysis on the anti-depressive effect included 10 studies. The meta-analysis showed that lavender was superior to placebo or no treatment comparators with the mean effect of -0.43 (95% CI -0.59 to -0.27) (Figure 3C). The meta-analysis showed that lavender was superior to control treatment significantly in 7 out of 10 RCTs with the treatment effects ranging -0.18 to -1.2. The statistics of heterogeneity showed a significant medium size heterogeneity (I^2=47%, p=0.05).

Risk of bias across studies

To evaluate potential publication bias, funnel plots were drawn and then Egger's regression test were performed for self-rated anxiety and depression respectively (see Funnel plots in Supplementary material, Appendix C and D). The funnel plot for standard error and effect sizes on anxiety seemed somewhat asymmetrical, seemingly empty in the lower-right

area. However, Egger's regression showed no evidence of significant publication bias (t=-1.04, df=28, p=.308). Egger's regression on depression also showed no evidence of publication bias (t = -1.61, df = 8, p = .146).

Because the publication biases for both anxiety and depression showed no significant evidence of biases, the results of our meta-analyses on anxiety and depression could be regarded as representative of the population of all published studies.

Additional analysis

Though the overall effect of the lavender treatment on self-rated anxiety levels showed significant medium to large size ($\hat{g}$ = -0.72, 95%CI: -0.90 to -0.55), the effect sizes of individual studies around the mean effect showed substantial variability. The heterogeneity statistics showed I^2=84%, Chi^2 = 104.75, df=29, and p>0.001. Intervention effects are often heterogenous across study characteristics including populations, interventions, comparisons, measures of outcomes, and methodological features. These study factors can moderate the effects of interventions and be sources of heterogeneity in combined effects.

Subgroup and moderator analyses can be done for the purpose of investigating heterogeneous results, or to explore specific questions about particular patient populations, methods of intervention or quality of study [29]. In subgroup analysis the test of significance indicates whether effects were significant within subgroups, not whether differences in effects were significant between subgroups. Moderator analysis provides tests of the differences in effects between subgroups and influences of moderators on the overall effect. The two statistical methods for moderator analysis are meta-analysis of variance (ANOVA) and meta-

regression, both approaches require at least 10 studies for each moderator to ensure statistical power of the analysis.

We hypothesized in the protocol that the effects of lavender could vary with study characteristics including routes and sessions of administration of lavender, health conditions of populations, and methodological quality, but the number of included studies in the meta-analysis for anxiety levels was 30, we conducted three moderator analyses including 1) the routes and 2) sessions of administration, and 3) health conditions of populations. The results of subgroup/moderator analysis for the anxiolytic effect are presented in Table1A.

The subgroup analysis by the route of administration showed that the application of lavender using massage, inhalation, and oral administration (silexan) were significantly superior to standard care, placebo or no treatment comparators. The mean effect of lavender inhalation was -0.83, and the effect of lavender using massage was -0.60, and silexan showed the smallest effect of -0.41.

The moderator analysis using meta-ANOVA to test statistical significance for different mean effects between routes of lavender indicated no statistical significance ($Q_b(df)=3.35(2)$, $p_b=.187$). To examine the possible impact of the route of administration for the heterogeneity of the overall effect of lavender on anxiety, we conducted additional moderator analysis using meta-regression. Meta-regression can be used to assess the potential impact of one or more continuous or categorical moderators. Categorical variable of the route of administration was expressed as a set of dummy variables with one omitted category in the meta-regression. Therefore, our meta-regression showed that routes of administration accounted 6.5% for the heterogeneity of the mean effect, the result showed no significance just the same as the statistical result of meta-ANOVA.

As the statistical power of moderator analysis is affected by the number of studies and the number of moderators, we should be cautious to interpret the results. The moderator analyses displayed meaningful results that meta-ANOVA showed that treatment effects according to the routes of administration were clearly different and the meta-regression indicated the route of administration accounted 6.5% for the variance of mean effect. But both moderator analyses showed no statistical significance, we can consider the possibility of the lack of statistical power by insufficient number of studies in the analyses.

The subgroup analysis for the effect of lavender on anxiety by health conditions of populations showed that the mean effect was -0.79 (95%CI:-1.05,-0.53) for populations undergoing surgery or invasive treatment, -1.00 (-1.35,-0.64) for the populations with coronary diseases or admitted in ICU group, -0.53 (-0.90, -0.15) for healthy population and -0.41 (-0.83, 0.02) for populations in anxiety and/or depression conditions. Lavender aromatherapy showed the largest efficacy in population with coronary diseases and/or patients in ICU and the efficacy for population with anxiety and/or depression showed the smallest and no statistical significance.

We performed both meta-ANOVA and meta-regression to explore possible influence of health conditions of populations on the variation of the mean effect. The meta-ANOVA indicated that different mean effects between health conditions of population were not statistically significant (Qb(df)=5.63(3), p_b=.131). The mean effects of subgroups of health condition of population were considerably different and the meta-regression showed that health conditions of population accounted 8.9% for the heterogeneity in mean effect (QM(df=3)=5.63, p=.131), but both moderator analyses showed no statistical significance. This might be ascribable to possible lack of power due to insufficient number of studies.

The meta-regression to test moderating effect of sessions of treatment showed that sessions of intervention accounted 13.18% for variations of mean effects significantly (QM=3.68, df=1, p=0.05). Regression coefficient of sessions was *b*= 0.0057, the regression equation can be suggested as *Y* = 0.0057*sessions – 0.82. This result means that the more sessions of treatment makes the larger effect sizes on anxiety.

Consequently we could explain the moderators such as above mentioned route of administration of lavender and health states of population and sessions of administration can reasonably influence the variability of the mean effect, only the test of statistical significance failed due to possible insufficient statistical power. Random effect model easily conclude non significance.

We performed a subgroup and moderator analysis to test the different means of anti-depressive effects by routes of administration (Table1B). The subgroup analysis showed the mean effect of inhalation on depression was -0.43 (95% CI -0.77 to -0.08), mean effect of massage was -0.63 (95% CI -1.08 to -0.17), mean effect of silexan was -0.42 (95% CI -0.72 to -0.12). Lavender tea showed no significant effect and effect size was the smallest (-0.32).

The moderator analysis by meta-ANOVA indicated that the different mean effects between inhalation, massage, tea, and silexan was not significant (Q=0.95, df=3, p_b=0.814). And also, the meta-regression indicated that the route of administration did not account for heterogeneity in mean effect (0%).

Finally we performed sensitivity analysis to examine whether the risk of within study bias influence the mean effect of lavender on anxiety (Figure 4). Specifically to examine the inclusion of studies at high overall risk impact the mean effect, we estimated the mean effect after deleting each study at high overall risk.

According to sensitivity analysis the mean effect changed to -0.68 from -0.66 after deleting the study of Bekhradi [30], -0.66 after deleting Hosseini [31], -0.65 after deleting Senturk [32], -0.68 after deleting Yayla [33], and -0.62 after deleting Zabirunnisa [34] respectively. Consequently, deleting each study at high overall risk did not change the mean effect significantly. So the mean anxiolytic effect of lavender demonstrated relatively robust and does not seem to be sensitive to the inclusion of the studies at high risk.

Discussion

Summary of evidence

The use of lavender essential oil has become popular in aromatherapy, and its therapeutic efficacy has been assessed in a large number of clinical trials. Aromatherapy with lavender essential oil was found to be effective in decreasing anxiety and its co-morbid depression in various settings. Physiologic parameters did not demonstrate consistent effects among parameters. Lavender showed significant decrease in systolic blood pressure, but did not affect diastolic blood pressure, heart rate and salivary or serum cortisol significantly.

Our meta-analysis demonstrated that lavender is superior to controls including standard care, placebo or no treatment in decreasing self-rated anxiety in diverse populations. The overall risk of bias in the primary studies assessed with revised ROB tool displayed that 5 of 37 studies were rated as high risk. But judging from the sensitivity analysis deleting each high risk study did not change the mean effect distinctly, implying the effect sizes of high risk studies might not be overestimated. Consequently, the overall effects demonstrated relatively robust and does not seem to be influenced by study quality of the included studies.

Our meta-analysis confirmed the results of Kang and colleagues [22] and Donelli and colleagues [24] in the efficacy for a significant decrease in anxiety, although the magnitude of effect varied slightly. The mean effect on anxiety levels of -0.72 can be interpreted as medium to large [35]. This effect is larger than the evidence (-0.65) of the review of Kang and colleagues [22], which synthesized 19 studies published 2000 to 2019. As the current review included 30 studies published from 2010 to 2019, the change of effect sizes between the reviews is noteworthy.

As our meta-analysis included studies administering routes of inhalation, massage, and oral silexan and also included studies comprising participants in diverse health states, the analysis demonstrated substantial heterogeneity in effects.

According to subgroup analysis by the route of administration, the effect size of inhalation was the largest other than massage and silexan. Our meta-analysis confirmed the results of Kang and colleagues [22] and Donelli and colleagues [24] in the efficacy of inhalation for a significant decrease in anxiety, although the magnitude of effect varied slightly. The effect estimate of inhalation (-0.83) is slightly larger than other evidences -0.71 [22] and -0.73 [24]). The result of our review and previous reviews suggest that inhalation of lavender oil is effective in decreasing anxiety levels in high anxiety inducing situations considerably. The inhalation of lavender essential oil can be recommended as efficacious intervention to decreasing anxiety in people in diverse situations of anxiety.

The massage with lavender oil showed medium to large anxiolytic effect (-0.60). This effect estimate is similar to other evidences (-0.61 [22], -0.66 [24]). Therefore combined with the previous evidences the massage with lavender oil can be interpreted to have substantial effect of relieving anxiety for populations in anxiety conditions.

The oral lavender silexan also confirmed a significant anxiolytic effect. The included studies in meta-analysis for silexan showed high study quality of all low risk in overall risk of bias. The result confirms the evidences of Kang et al [22], Donelli et al [24], and Möller et al [23], although the magnitude of effect are different slightly and the effect measures are different (Hedges' ĝ versus weighted mean difference).

The analysis for publication bias by funnel plot and Egger's regression showed no evidence of publication bias, which signify our sample of meta-analysis may be representative the population of published studies on this topic. Consequently, the evidence of the anxiolytic effect of lavender can be interpreted as fairly robust considering the quality of research designs, no evidence of publication bias, and confidence intervals that do not cross the line of no effects.

Vital signs and salivary cortisol are recognized as important physiological measures that indirectly indicate anxiety. Our results indicated that lavender has a decreasing effect on SBP. The effect size is small, but it can be interpreted as meaningful change, because systolic blood pressure may be difficult to change. The risk of bias of included studies on physiologic measures was low, as the effects of these outcomes would not be affected by participants' awareness of intervention. Therefore, study quality might not influence treatment effects. In conclusion, the the effect of lavender on blood pressure is small but not weak, based on consistent effect sizes, significant effect, and strong study quality.

The efficacy of lavender on diastolic pressure, heart rate showed small effect sizes of -0.15 and -0.20, and no significant effects. The effect of cortisol was -1.4 with no statistical significance. We can interpret that there is no evidence that the mean effect is statistically different from no effect. However, no evidence of an effect is not the same as evidence of no effect, that is to say, no significant effects do not prove that there is no effect. An alternative explanation may be due to too small sample size or too much heterogeneity. The results of

DBP, heart rate, cortisol can be attributed to insufficient statistical power due to overly few studies, because statistical power is affected by the number of studies in the meta-analysis. Therefore, we recommend future studies of RCTs investigating the anxiolytic efficacy of lavender on physiologic or endocrinological stress markers such as vital signs or cortisol.

Depression has been recognized as a major co-morbidity symptom of anxiety. Our results demonstrate that lavender has a favorable relieving effect on depression levels. The mean effect was medium effect size according to Cohen's standard [35]. Subgroup analysis indicated that route of lavender application tea, massage, and silexan showed significant anti-depressive effects and massage with lavender demonstrated the largest effect size. Only inhalation showed no significant effect. The evaluation of risk of bias across studies indicated that there is no evidence of publication bias. This evidence on anti-depressive effect of lavender are not able to be compared to other evidence because published evidence on this topic could not be located.

In conclusion, lavender aromatherapy by means of massage, silexan, or tea significantly decreases depression in people with various health conditions. There is some evidence of the efficacy of lavender on depression levels, on the grounds that there was no evidence of publication bias, and the quality of studies showed no evidence of impact on the observed effect.

Limitations

To ensure study quality, we synthesized only RCTs on the effect of lavender on anxiety and depression; however, the risk of bias assessment showed that of all 37 studies included in quantitative analysis, 16 were rated as some concern of risk and 5 studies were evaluated as high risk of overall risk of bias. Only 16 of 37 studies were at low risk of bias. Outcomes such

as self-rated anxiety or depression can be influenced by outcome assessor's knowledge of intervention received. Therefore, our results on anxiety and depression could have been influenced by participants' knowledge of the intervention received, for example inhalation of lavender or massage using lavender oil.

Though the evaluation of publication bias in our quantitative analysis showed no evidence of risk of bias across studies, in our review process we included only studies written in English, published reports, and accessible reports based on preset inclusion criteria. These limits in the locating and screening process might have introduced sampling bias.

Conclusions

Our meta-analysis confirmed the results of existing reviews on the effect of inhalation and massage applicating lavender essential oil for a significant decrease in anxiety levels, although the magnitude of effect varied slightly. The effect of silexan also confirmed a significant anxiolytic effect of previous evidences.

The effects on physiologic parameters including diastolic blood pressure, heart rate, and salivary or serum cortisol showed small in effect sizes and no evidence of significant effects. Only systolic blood pressure displayed significant small effect size. The statistical power of the analyses on physiological parameters might be weak due to overly small samples, and magnitude of effects were small. Therefore, more and larger randomized trials testing the effect of lavender aromatherapy for anxiety measured with physiologic measures including vital signs or cortisol are recommended.

Our analysis on the effect of application of lavender for the treatment of depression demonstrated a beneficial effect on decreasing depression. The effect size on depression cannot

be compared to the literature, because published data on this topic could hardly be located. Our review included any type of participant, method of intervention, or outcome measure in primary studies investigating the efficacy of lavender aromatherapy. We recommend future reviews focusing on populations in specific health conditions and routes of application of lavender.

Conflict of Interest: None.

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Table 1A. Subgroup/moderator Analyses for the Impact of Study Characteristics on Anxiolytic Effect of Lavender

Moderators/subgroups	k	Hedges' ĝ	95% CI	Q_b (df)	p_b
Route of administration					
Massage	5	-0.60	-1.02, -0.18	3.35(2)	.187
Inhalation	21	-0.83	-1.03, -0.62		
Silexan 80mg	4	-0.41	-0.84, 0.03		
Meta-regression			QM(df = 2) = 3.35, p = .187		
			R^2 (amount of heterogeneity accounted for): 6.5%		
Health condition of populations					
Surgery or invasive	13	-0.79	-1.05, -0.53	5.63(3)	.131
Coronary ICU	7	-1.00	-1.35, -0.64		
Healthy	6	-0.53	-0.90, -0.15		
Anxiety or depression	4	-0.41	-0.83, 0.02		
Meta-regression			QM (df=3)=5.63, p = .131		
			R^2 (amount of heterogeneity accounted for): 8.9%		
Overall risk of within-study bias					
Some concern	14	-0.81	-1.08, -0.53	0.68(2)	.713
Low	11	-0.64	-0.93, -0.34		
High	5	-0.74	-1.20, -0.28		
Meta-regression			QM (df = 2) = 0.68, p = .713		
			R^2 (amount of heterogeneity accounted for): 0.0%		
Sessions of intervention					
Meta-regression			QM(df = 1) = 3.68, p = .055		
			R^2 (amount of heterogeneity accounted for): 13.2%		
Overall effect	k	Hedges' ĝ	95% CI	Q (df)	p	I^2
	30	-0.72	-0.90, -0.55	184.75(29)	< .001	84.3%

Note. CI=confidence interval, df=degree of freedom, ICU=intensive care unit, Q_b= Q between groups, QM=Q moderator, $p_b = p$ between groups.

Table 1B. Subgroup/Moderator Analysis on the Impact of the Route of Administration on Anti-depressive effects of lavender

Moderator/subgroup	k	Hedges' ĝ	95% CI	Q_b (df)		p_b
Route of administration						
Inhalation	3	-0.42	-0.77, -0.08			
Tea	2	-0.32	-0.76, 0.12			
Massage	2	-0.63	-1.08, -0.17	0.95(3)		.814
Silexan 80 mg	3	-0.42	-0.72, -0.12			
Meta-regression			QM(df = 3) = 0.95, p = .814			
			R^2 (amount of heterogeneity accounted for) : 0.0%			
Overall effect	k	Hedges' ĝ	95% CI	Q (df)	p	I^2
	10	-0.43	-0.59, -0.27	16.88 (9)	.051	46.7%

Note. CI=confidence interval, df=degree of freedom, Q_b = Q between groups, QM= Q moderator, $p_b = p$ between groups

Figure legends

Figure 1. Flow diagram of the study selection process

Note. RCT = randomized controlled trial; SD = standard deviation

Figure 2A. Risk of bias summary according to the revised Cochrane risk-of-bias tool for randomized trials (R0B 2)

D1 : Randomization process;

D2 : Deviations from intended interventions;

D3 : Missing outcome data;

D4 : Measurement of the outcome;

D5 : Selection of the reported result

Figure 2B. Risk of bias graph according to the revised Cochrane risk-of-bias tool for randomized trials (R0B 2)

Figure 3A. Forest plot on the efficacy of lavender on self-rated anxiety levels

*Note.*CI= confidence interval; SMD=standardized mean difference

Figure 3B. The effect of lavender on physiological parameters

*Note.*CI= confidence interval; *df*=degree of freedom; IV=inverse variance; SD=standard deviation;

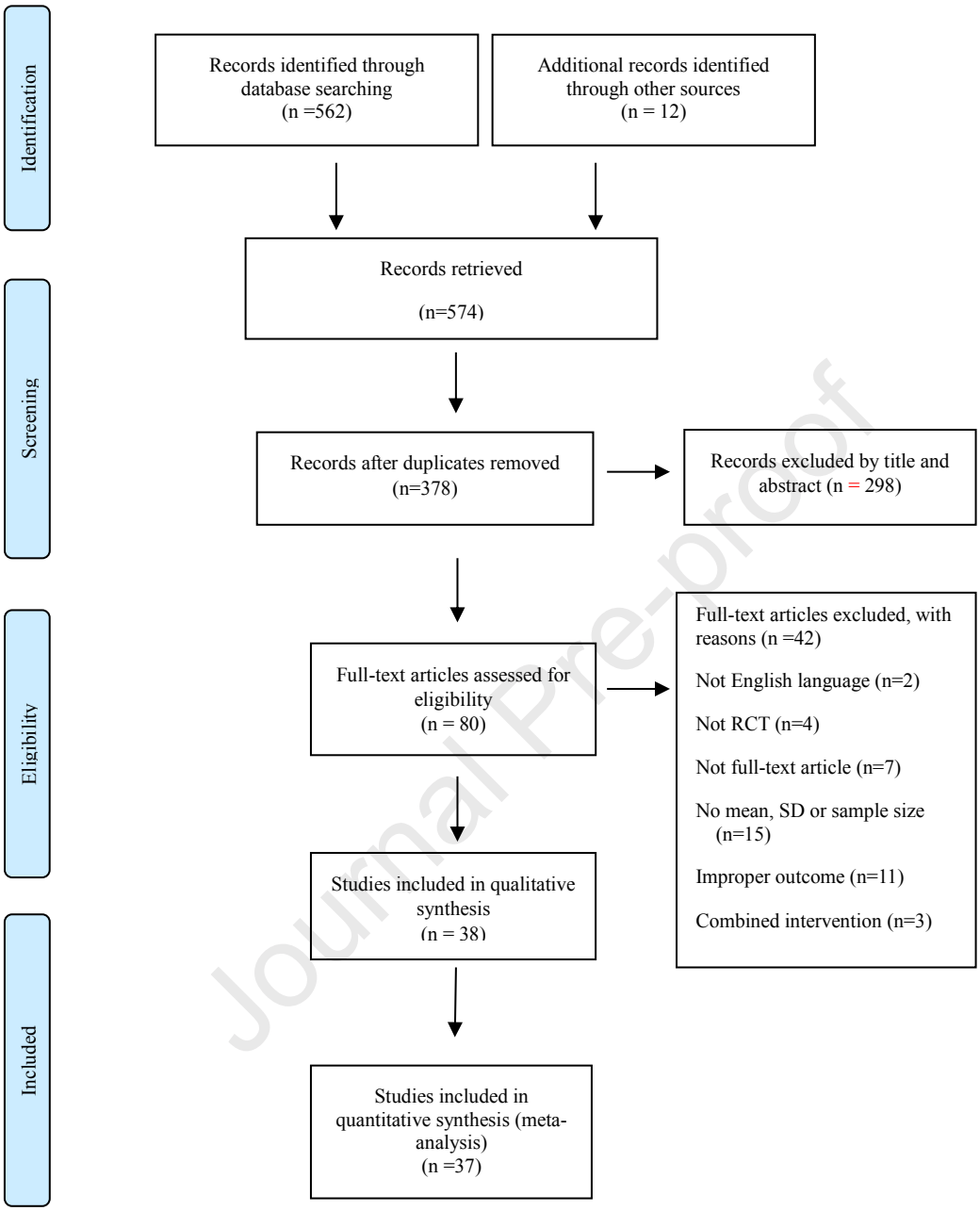
SBP: systolic blood pressure ; DBP: diastolic blood pressure; HR: heart rate

Figure 3C. The effect of lavender on depression levels

*Note.*CI= confidence interval; *df*=degree of freedom; IV=inverse variance; SD=standard deviation

Figure 4. Sensitivity analysis : The mean effect after dropping each study at high overall bias for anxiety levels; studies enclosed by square dotted line are at high overall bias.

Note. CI = confidence interval; SMD = standardized mean difference



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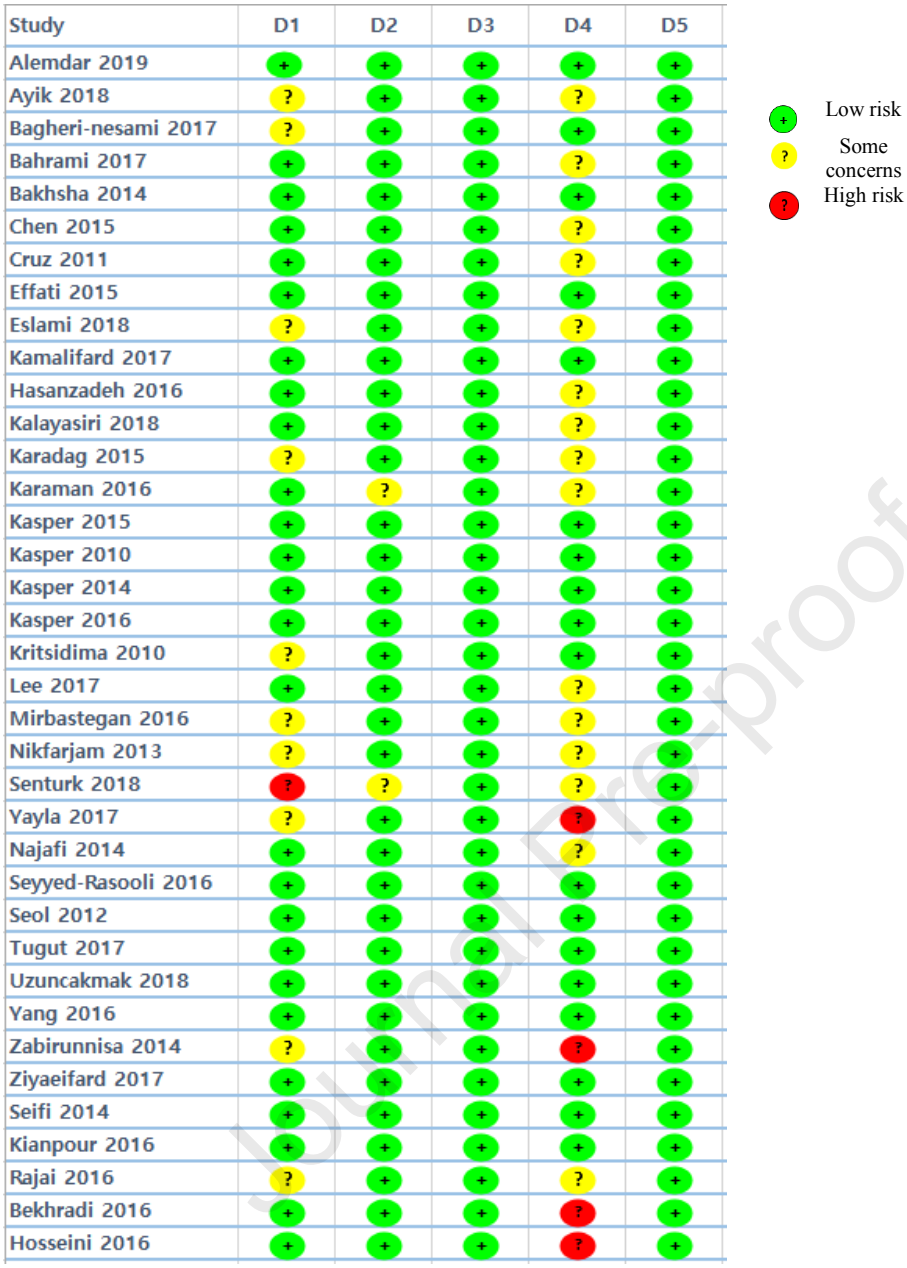

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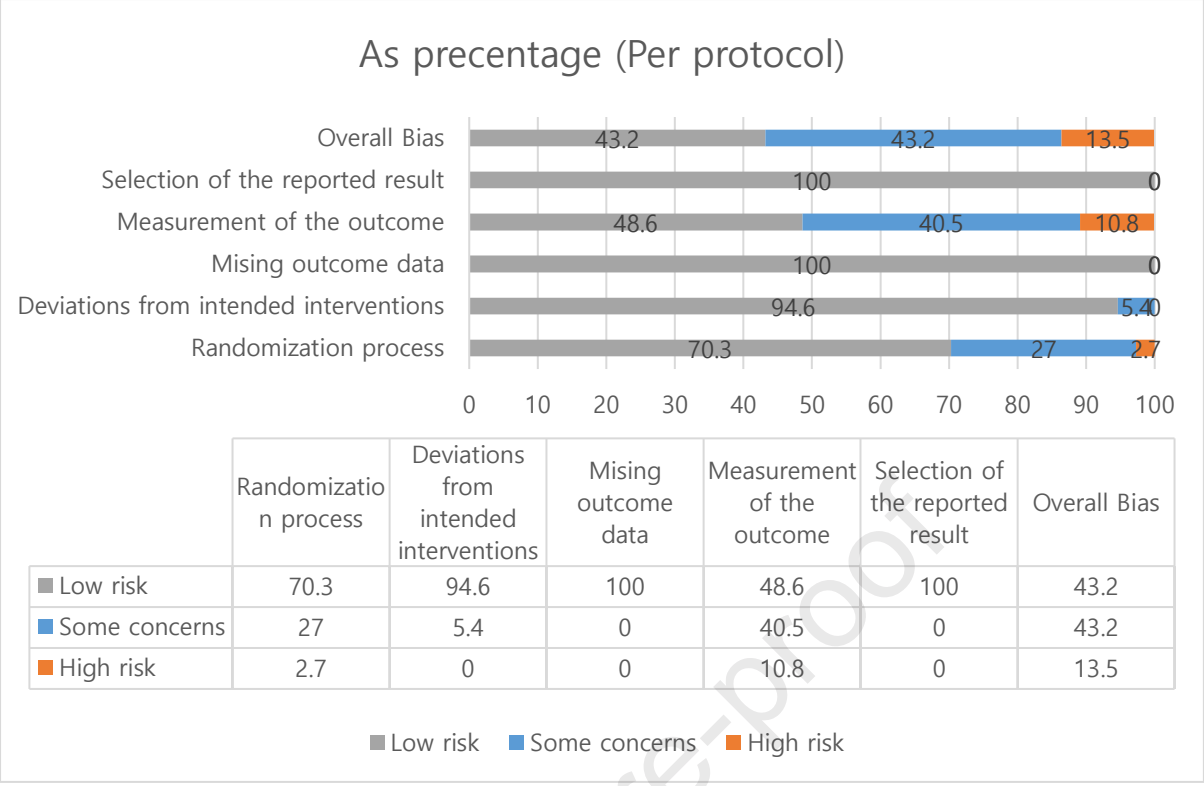


	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Low risk	70.3	94.6	100	48.6	100	43.2
Some concerns	27	5.4	0	40.5	0	43.2
High risk	2.7	0	0	10.8	0	13.5

Figure 2B. Risk of bias graph according to the revised Cochrane risk-of-bias tool for randomized trials (R0B 2)

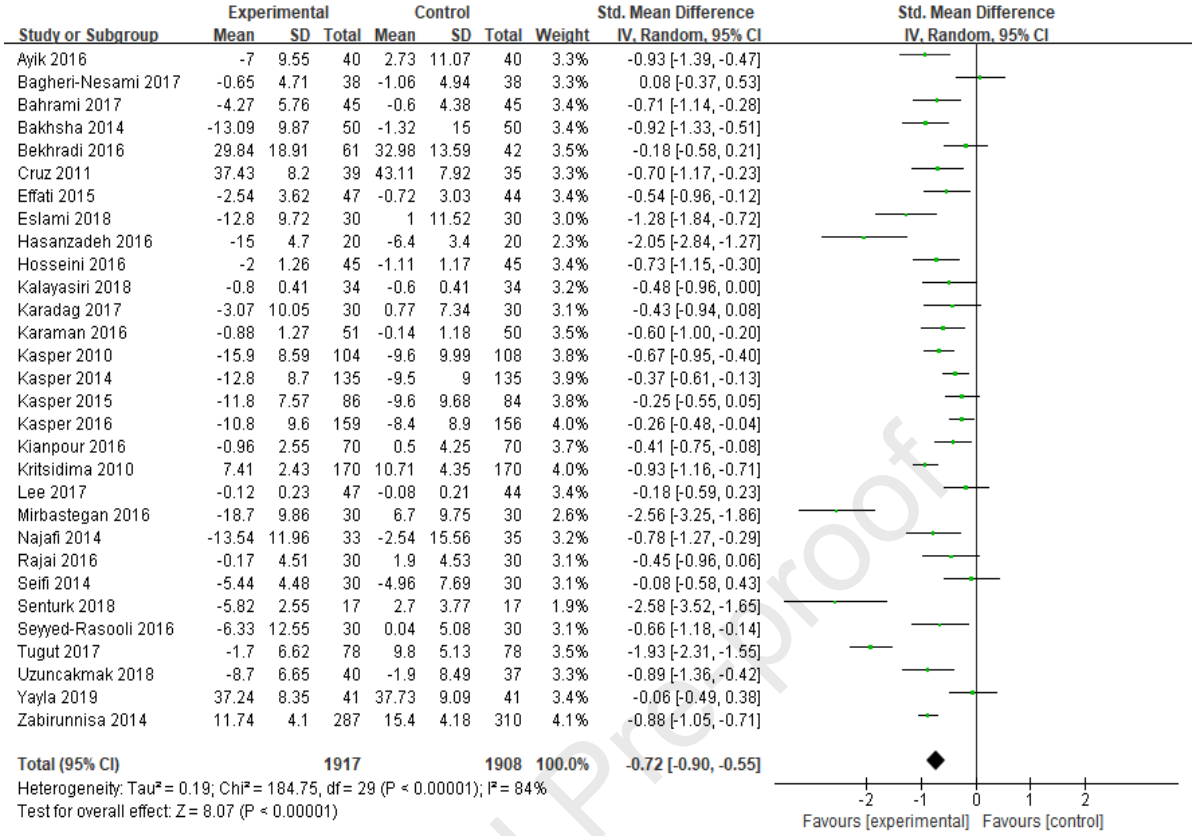
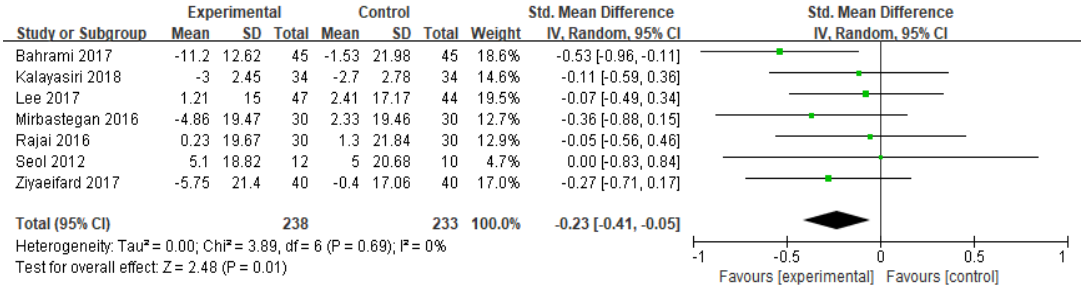


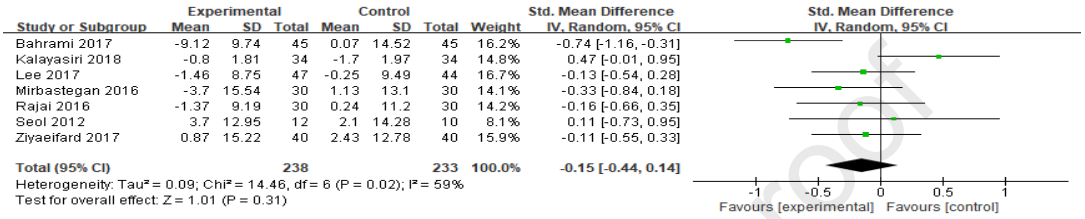
Figure 3A. Forest plot on the efficacy of lavender on self-rated anxiety levels

Note.CI= confidence interval; SMD=standardized mean difference

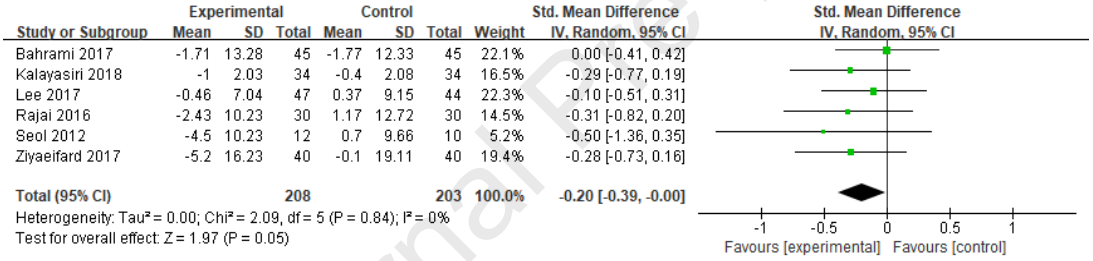
SBP



DBP



HR



Serum/salivary cortisol

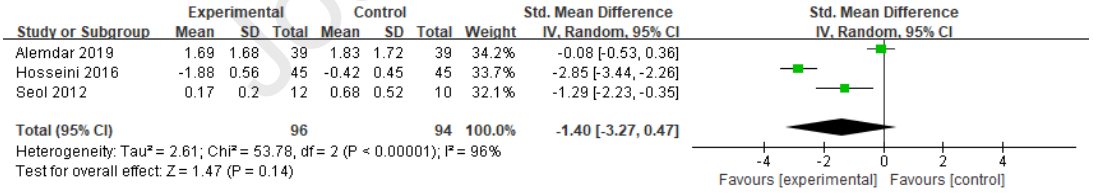


Figure 3B. The effect of lavender on physiological parameters

Note.CI= confidence interval; *df*=degree of freedom; IV=inverse variance; SD=standard deviation;

SBP: systolic blood pressure ; DBP: diastolic blood pressure; HR: heart rate

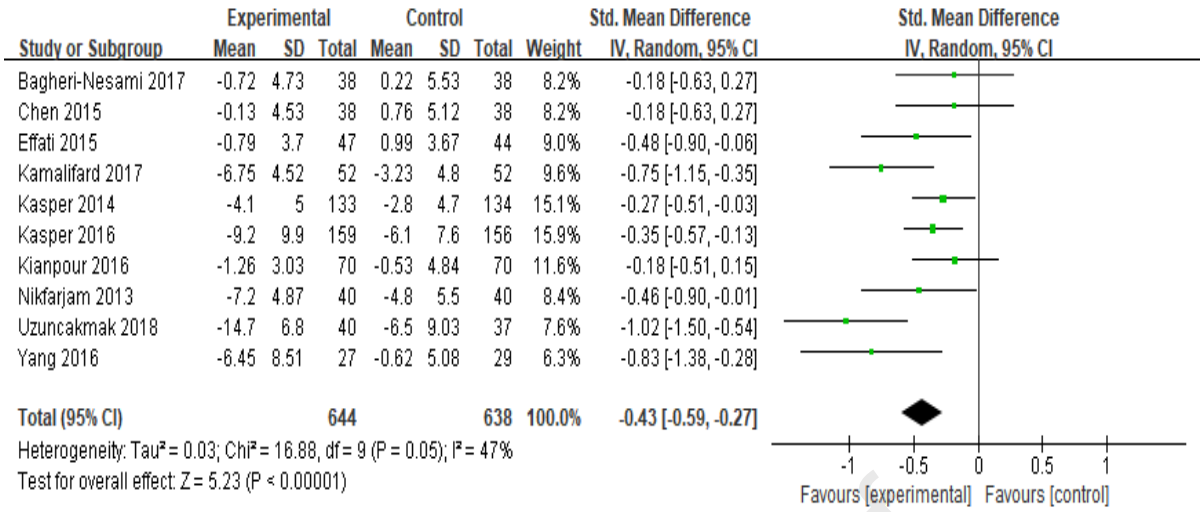
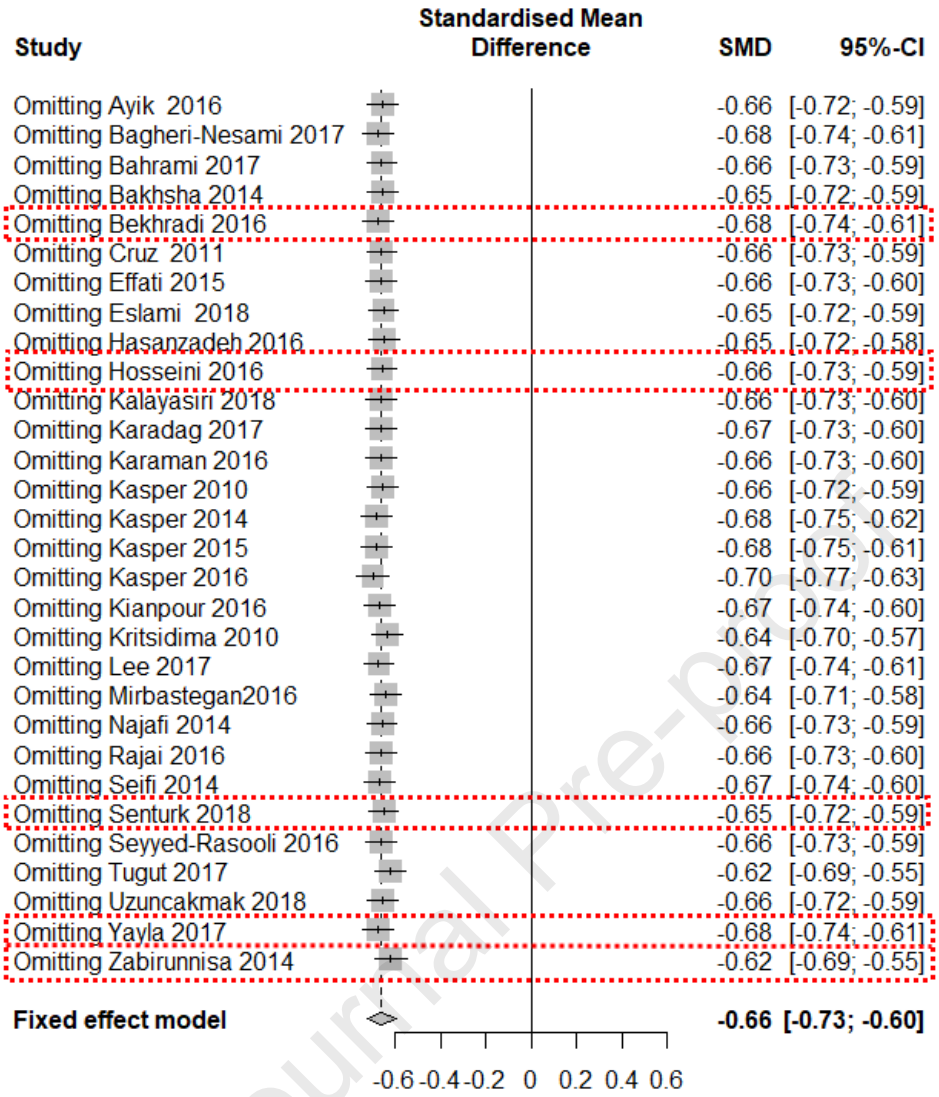


Figure 3C. The effect of lavender on depression levels

Note.CI= confidence interval; *df*=degree of freedom; IV=inverse variance; SD=standard deviation



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