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Essential oil of lavender in anxiety disorders: Ready for prime time?

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Abstract

Anxiety disorders are some of the most common psychiatric disorders, with potentially debilitating consequences on individual function. Existing pharmacotherapies for anxiety disorders are limited by delay to therapeutic effect, dependence, tolerance, withdrawal, and abuse potential. Therefore, safe and evidence-based complementary or alternative therapies may be important allies in the care of patients with anxiety disorders. Essential oils are lipophilic and concentrated botanical extracts that exhibit many properties of drugs, although they are not Food and Drug Administration approved and have limitations characteristic of herbal preparations. Lavender essential oil has an extensive anecdotal history of anxiolytic benefit that has recently been supported by clinical efficacy studies. The 2 primary terpenoid constituents of lavender essential oil, linalool and linalyl acetate, may

produce an anxiolytic effect in combination via inhibition of voltage-gated calcium channels, reduction of $5HT1_A$ receptor activity, and increased parasympathetic tone. The objectives of this article are to provide a brief overview of lavender oil in aromatherapy, explore variability in the constituents of lavender oil, summarize its pharmacology and safety profile, as well as describe its body of research that has been conducted for anxiety.

Keywords: lavender, essential oil, linalool, linalyl acetate, Silexan, anxiety, stress, complementary and alternative medicine

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Background

Anxiety disorders are prevalent psychiatric conditions that can be debilitating in many patients and include phobia, panic, general anxiety (GAD), and separation anxiety disorders.[1] It is estimated that the 12-month prevalence of anxiety disorders is about 10% in the adult population and that females are twice as likely to have an anxiety disorder in comparison with males.[2,3] Afflicted individuals typically exhibit both psychiatric and somatic symptoms, with depression, sleep disturbance, and substance use disorders being common comorbidities.[4-6] Current anxiolytic treatment options have limitations in efficacy, such as delay to onset (eg, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, buspirone) as well as habituation, tolerance, and abuse potential (eg, benzodiazepines, pregabalin). Other limiting factors include side effects, like sedation (eg, hydroxyzine, benzodiazepines) and withdrawal syndromes (eg, benzodiazepines, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors).[7] Even when used appropriately, anxiolytic agents may lack efficacy or only be partially effective in controlling symptoms, warranting the consideration of complementary or alternative treatment options.

Essential oil (EO) of lavender (LEO; *Lavandula angustifolia*) is purported to be antibacterial, antifungal, anxiolytic, antidepressant, analgesic, carminative (smooth-muscle relaxant), as well as to have beneficial immunomodulatory effects on wound healing.[8-10] Folkloric claims of benefit in anxiety have been supported recently by clinical data, while other studies have produced inconclusive or equivocal results. Although whole-plant formulations may not provide adequate concentrations of active ingredients for effect, EOs are concentrated lipophilic extracts of aromatic terpenoid constituents. They are able to traverse cell membranes and exhibit pharmacologic effects at nanomolar concentrations, making them *druglike* and increasing suitability for potential pharmaceutical application.[11] The objectives of this article are to provide a brief overview of lavender oil in aromatherapy, explore variability in the constituents of lavender oil, summarize its pharmacology and safety profile, and describe its body of research that has been conducted for anxiety.

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Lavender Oil and Aromatherapy

Historically, EOs have been delivered as aromatherapy via inhalation or topical routes. Essential oils delivered via inhalation route may exert psychologic effects, because the olfactory bulb has limbic inputs in the amygdala and hippocampus that are associated with emotion and memory.[12] It is hypothesized that smell-triggered emotional memory may be the etiologic root of situational anxiety in some circumstances. This form of emotional memory is exemplified by state anxiety associated with the characteristic smell of the dentist's office, which has been reduced with LEO.[13] Conversely, particular smells may be associated with positive emotions and mood, which is a core tenet of hypothesized benefits in aromatherapy.

Studies of aromatherapy pose significant challenges to highly rigorous research because of the inability to blind investigators and

participants from the scent of the EO or control topical massage, confounding any observed benefit. Many small, randomized trials of aromatherapy have been performed in medical settings that may provoke anxiety, although the participants who were included had not received a diagnosis of an anxiety disorder at baseline. Reduction of state anxiety in such situations as preoperative anxiety, chest tube removal, cosmetic procedures, and intensive care unit stays, were reported.[14-18] However, other similarly designed studies[19-22] in similar settings have failed to show benefit or have not demonstrated clear benefit. A single observational pilot study[23] in postpartum women with anxiety demonstrated reduced anxiety levels using a rose/lavender oil blend for 15 minutes twice weekly during the course of 4 weeks. One study[24] concluded that participant expectation of relaxation was a greater factor than LEO itself, highlighting the expectation bias to which aromatherapy studies may be subject to despite blinding.

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Variability in Lavender Oil Constituents

Essential oils, including LEO, are complex compositions of compounds that may contain up to several hundred distinct chemical entities. They vary in constituents in a manner similar to that of herbal products, because the aromatic compounds produced are a function of the botanical products' genetics, growth conditions, and oil extraction process. Gas chromatography–mass spectrometry has aided in untangling which constituents occur most frequently, allowed insight into variability among LEOs, and given clues about which constituents may be primarily active. For example, one analytic study found varying concentrations of linalool (26.73%-57.48%) and linalyl acetate (4.01%-35.39%) among 9 different LEO samples.[25] This concentration variability leads to significant heterogeneity in products used in different studies and adds to the difficulty in delineating results.

In Germany, a standardized essential oil extract of *Lavandula angustifolia* (SLO) for oral administration has been developed and approved for use in subsyndromal anxiety. The SLO product (Silexan, W. Spitzner Arzneimittelfabrik GmbH, Ettlingen, Germany), contains the 2 primary constituents of lavender oil—linalool and linalyl acetate—at concentrations of 36.8% and 34.2%, respectively.[11] Although SLO has consistent amounts of linalool and linalyl acetate, they comprise only 71% of the oils' overall composition, leaving room for variation in constituents that occur in lower concentrations. The SLO product is available in 80-mg gel capsules for once- or twice-daily administration and is marketed as an over–the-counter dietary supplement called Calm Aid in the United States. The use of a standardized oral formulation in SLO has greatly increased the ability to study lavender oil with a high degree of methodologic rigor, including through randomized, double-blinded, placebo-controlled studies. Although not the intended focus of this article, SLO provides the highest-quality clinical evidence currently available for LEO.[26,27]

Although SLO is standardized to 80 mg, a similar dose size can be calculated readily using a nonstandardized LEO. The density of lavender oil has been estimated to be around 0.88 g/mL at 20°C.[28] Therefore, 0.1 mL of oil would be weigh approximately 88 to 89 mg. Assuming 20 drops per milliliter, this would equate to around 2 drops of LEO for a dose of 88 mg, although variability is to be expected given the imprecise nature of this calculation, and it may be more accurate to measure a volume or directly weigh the oil.

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Mechanism of Action

A few lines of inquiry have helped to elucidate potential mechanism(s) of action of LEO in anxiety-related conditions, which appears to be related to inhibition of voltage-gated calcium channels (VGCCs),

reduction of $5HT1_A$ receptor activity, and increased parasympathetic tone. A purely psychologic mechanism has been refuted in the case of LEO's anxiolytic effects because anosmic mice display inhibition of marble burying after lavender oil inhalation.[29] Pharmacokinetic data after topical application in healthy human volunteers also demonstrated the ability of LEO's constituents linalool and linalyl acetate to rapidly penetrate cell membranes and reach serum concentrations in excess of 100 ng/mL, corroborating pharmacodynamic action.[30]

In mice, SLO was used along with diazepam, pregabalin, and other essential oil–based terpenes as active controls to investigate pharmacodynamic properties. The SLO lacked appreciable affinity for serotonin, norepinephrine, or dopamine reuptake transporters, as well as monoamine oxidase-A or γ-aminobutyric acid-A receptors, suggesting a novel mechanism compared with traditional anxiolytic therapies. Linalool and linalyl acetate displayed inhibitory activity on Ca^{2+} influx mediated by VGCCs in murine synaptosomes as well as primary hippocampal neurons with an estimated IC_{50} of 37 nM for linalool. In contrast to pregabalin, which exerts inhibition of Ca^{2+} influx via interaction with α2δ-1 and α2δ-2 subunits of P/Q type VGCCs, SLO did not bind with these subunits, although it did produce a nonspecific decrease in Ca^{2+} influx across N, T, and P/Q type VGCCs, suggesting a truly unique mechanism.[11]

A randomized, blinded, placebo-controlled crossover trial[31] in 17 healthy human volunteers investigated brain changes detectable by positron emission tomography and magnetic resonance imaging scanning after administering 8 weeks of SLO at 160 mg/d. The investigators focused on the inhibitory $5HT_{1A}$ receptor because of increases in activity of this receptor being highlighted in the pathophysiology of anxiety in previous neuroimaging studies.[32] They found reduced binding potential at the $5HT_{1A}$ receptor in the hippocampus and the anterior cingulate cortex in the SLO group

compared with placebo, which has also been demonstrated after administration of escitalopram or electroconvulsive therapy in patients with anxiety.[31,33] The authors postulate that reductions in $5HT_{1A}$ receptor activity may be a commonality in the anxiolytic efficacy of various interventions, and that SLO also acts via this mechanism.

Additional to central effects, lavender oil appears to have peripheral effects that may be important to its mechanism of action. Lavender oil has displayed increased parasympathetic activity as well as decreased hemodynamic parameters in rats, dogs, and humans.[34-38] These effects may help alleviate somatic symptoms of anxiety characterized by autonomic arousal, although they may introduce pharmacodynamic interaction potential with antihypertensive or central nervous system depressant agents.

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Pharmacokinetics

Linalyl acetate is a carboxylated ester and metabolized to linalool by β-esterases, which are mostly found in hepatocytes but are also found in the periphery. Linalool is metabolized primarily through conjugation with glucuronic acid and is oxidized by cytochrome P450 enzymes (CYP450). Linalool is excreted primarily in urine but is also excreted via feces and in expired air.[39]

Two clinical drug interaction studies[40,41] have been conducted using SLO. One was conducted in 16 healthy volunteers who were administered SLO 160 mg/d for 11 days in a double-blind, randomized, placebo-controlled, crossover fashion.[40] Various drugs were used for phenotyping effects on CYP enzymes, with no clinically relevant inhibition or induction found on CYP 1A2, 2C9, 2C19, 2D6, and 3A4 enzymes. The second was a double-blind, randomized, placebo-controlled, crossover trial conducted in 24 women taking oral contraceptives during two menstrual cycles.[41] No changes in area

under the curve or maximum serum concentration (C_{max}) values of ethinyl estradiol or levonorgestrel were discovered, and there were no changes in secondary outcomes that may indicate impairment of oral contraceptive efficacy. However, the time to maximum concentration (T_{max}) for levonorgestrel was slightly delayed. Although this may not be clinically significant in the use of daily oral contraceptives, efficacy of emergency contraceptives in which efficacy is critically time dependent could be impacted.[41] Effects on glucuronosyltransferase have not been described.

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Safety and Tolerability

Lavender essential oil has been granted Generally Recognized as Safe status by the Food and Drug Administration (21CFR182.20 2015), which means that it is safe when used for its intended purpose as a food additive.[42] Many EOs are inappropriate for oral administration in their undiluted form because of irritant, inflammatory, or cytotoxic effects on skin and especially mucous membranes, warranting dilution or avoidance. LEO is seemingly well-tolerated in this regard and is often applied topically or administered orally in an undiluted form. Reports of in vivo contact dermatitis and in vitro cytotoxicity, however, exist, warranting caution.[43,44] Long-term studies demonstrating safety are lacking.

Reports of prepubertal gynecomastia in boys exposed to LEO have been reported, although these are far from conclusive.[45] LEO displayed very weak estrogenic and antiandrogenic activity in vitro, raising doubt as to whether the effects could actually induce gynecomastia.[46]

Poisoning by lavender is uncommon. In the late 1960s and early 1970s, the LD_{50} values for lavender taken orally and applied topically were determined. In mice, the oral LD_{50} was 13.5 ± 0.9 g/kg, where

central nervous system depression occurred 10 to 15 minutes following ingestion and death occurred 1 to 3 days later.[47,48] Similar results were observed in rats.[47] For dermal applications, the LD_{50} was greater than 5 g/kg, with no systemic symptoms or deaths in rabbits observed up to 14 days.[48] In humans, an 18-month-old boy ingested homemade lavandin (*Lavandula x intermedia*) extract. Three hours following the ingestion, the child developed confusion and deep drowsiness, with adaptive motor response to painful stimuli indicative of moderate brain injury (Glasgow Coma Score = 9). His neurologic status normalized within 6 hours of hospitalization, and a follow-up electroencephalogram was normal at 24 hours. Comparative toxicology analysis between the boy's blood, urine, and pure lavandin extract showed linalyl acetate, linalyl formate, and acetone were detected in all samples. Acetone, which was a confounding factor for coma in the poisoning, was found to be slightly higher than normal in healthy adults and was concluded not to be the cause of the central nervous system depression.[49]

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Efficacy in Anxiety Disorders

Medline and EMBASE searches were conducted between database inception and September 15, 2016. Search terms included *linalool or linalyl acetate or lavender oil or Lavandula angustifolia or Silexan* and *anxiety or stress*. Searches were conducted independently by one of the study authors (B.J.M.) as well as a medical librarian. Articles reviewed were randomized studies that enrolled at least 10 human participants with an anxiety disorder, featured an end point that measured anxiety, and were written in English. Review articles were screened for additional references.

Five double-blinded and randomized controlled trials using either placebo or active controls were identified that are summarized in the Table.[50-54] All trials were conducted in Germany, had a duration

of 6 to 10 weeks, and used the oral standardized lavender oil preparation SLO. Studies were conducted in an outpatient setting and were generally mixed between psychiatric and primary care practices. Some major strengths of the studies were adequate power to detect differences in treatments, use of both intention-to-treat and per protocol analysis sets, and prohibition of concomitant anxiolytic medications or psychotherapy during the study period. Participants were predominantly female (66%-77%), an average age of 45 to 49 years, white, and had a moderate to severe anxiety according to baseline Hamilton Anxiety Rating Scale (HAMA) scores. Psychiatric and neurologic comorbidities were generally excluded, including personality disorders, substance use disorders, and suicidality. Varying degrees of depressive symptoms were allowed, although this was study dependent. In all trials SLO was found to be efficacious in reducing HAMA scores (Table) and was well tolerated, with gastrointestinal side effects being the most commonly reported side effect.

TABLE:

Randomized controlled trials conducted with lavender essential oil in patients with anxiety disorders

Study	Study Design	Sample	Intervention	Primary Outcome	Main Result	Adverse Effects
Kasper et al[51] (2010)	DB with 2 parallel groups 27 General and psychiatric primary care centers in Germany	• Anxiety disorder NOS (DSM-IV) *subsyndromal anxiety disorder* • 216 Participants (SLO, 107; placebo, 109) • Baseline HAMA total score ≥18 points; PSQI >5	Capsules containing 80 mg of SLO or matching placebo: 1 PO daily × 10 wk	HAMA: score change from baseline to wk 10	HAMA: • Baseline: 26.8 ± 5.4 SLO; 27.1 ± 5.3 placebo ($P < .755$) • SLO decrease: 16.0 ± 8.3; placebo decrease: 9.5 ± 9.1 ($P < .001$)	GI-related side effects
Woelk and Schläfke[54] (2010)	DB with 2 parallel groups Outpatient general practitioners in Germany	• Patients with GAD (DSM-IV) • Average duration of illness: 4.5 ± 5.0 y • Baseline HAMA total score ≥18 points • 77 Participants (SLO, 40; lorazepam, 37)	Capsules containing 80 mg of SLO or lorazepam 0.5 mg: 1 PO daily × 6 wk	HAMA: score change from baseline to wk 6	HAMA: • SLO: baseline, 25.0 ± 4.0; week 6, 11.3 ± 6.7 • Lorazepam: baseline, 25.0 ± 4.0; week 6, 11.6 ± 6.6	SLO: eructation, dyspepsia, nausea Lorazepam: nausea, fatigue
Kasper et al[52] (2014)	DB with 4 parallel groups 57 Psychiatric and general practices in Germany	• Patients with GAD (DSM-5) • Average duration of illness 2.5 y, current episode 1 y • 536 Participants (SLO, 160 mg/d, 128; 80 mg/d, 135; paroxetine, 137; placebo, 136) • Baseline HAMA total score ≥18 points	Capsules containing 80 mg of SLO, matching placebo, or paroxetine: SLO 80 mg; 160 mg; paroxetine 20 mg; placebo PO daily × 10 wk	HAMA: score change from baseline to wk 10	HAMA: decreased 14.1 ± 9.3 SLO 160 mg/d ($P < .001$), 12.8 ± 8.7 SLO 80 mg/d ($P = .002$), 11.3 ± 8.0 paroxetine ($P = .096$), and 9.5 ± 9.0 placebo	No withdrawal-related symptoms measured in posttrial observation week
Kasper et al[50] (2015)	DB with 2 parallel groups 17 General and psychiatric practices in Germany	• Patients with restlessness, disturbed sleep, and subthreshold anxiety disorder (R45.1 ICD-10) • 170 Participants (SLO, 86; placebo, 84) • Baseline HAMA total score ≥18 points; PSQI ≥6; VAS ≥5 for agitation and restlessness	Capsules containing 80 mg of SLO or matching placebo: 1 PO daily × 10 wk	HAMA: score change from baseline to wk 10	HAMA: • Baseline: 25.5 ± 6.0; wk 10: 13.7 ± 7.0 • SLO decrease −12.5; placebo decrease −9 ($P = .01$)	Eructation, diarrhea, oral discomfort, gastritis (10.5%)
Kasper et al[53] (2016)	DB with 2 parallel groups 35 Psychiatric practices in	• Patients with MADD (ICD-10 F41.2) • 318 Participants	Capsules containing 80 mg of SLO or matching	HAMA: score change from baseline to wk 10	HAMA: • Baseline: 25.7 ± 5.6; week 10:	Eructation, nausea

Three of the studies[50,51,53] compared SLO 80 mg daily to placebo. One study[53] (n = 318) included patients with Mixed Anxiety and Depressive Disorder and measured both anxiolytic and antidepressant effects. Mixed Anxiety and Depressive Disorder is a World Health Organization International Classification of Diseases (ICD) diagnosis pertaining to patients suffering from anxiety with autonomic features and depressive symptoms of equal intensity without anxious or depressive symptoms being predominant. SLO was found to be efficacious in reducing HAMA scores (Table) as well as Montgomery-Asberg Depression Rating Scale Scores. Montgomery-Asberg Depression Rating Scale scores decreased from 22.0 at baseline to 12.8 ± 8.7 with SLO, compared with 22.1 ± 6.1 to 16.0 ± 9.8 with placebo, which corresponded with a mean difference of 3.53 (95% confidence interval: 1.36, 4.14; $P < .001$) in favor of SLO. The other two studies[50,51] evaluated the effect of SLO on HAMA along with sleep by measuring the Pittsburgh Sleep Quality Index (PSQI) at baseline and scheduled visits in patients with subsyndromal anxiety disorder, and anxiety and restlessness with disturbed sleep. Subsyndromal anxiety disorder includes patients with pronounced anxiety or phobic avoidance who do not meet criteria for a more specific anxiety disorder. It is a World Health Organization ICD diagnosis, although it was paralleled in *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, as anxiety not otherwise specified. Restlessness and agitation with disturbed sleep is an ICD-10 diagnosis falling under an umbrella of disorders involving signs and symptoms associated with a negative emotional state that is not well defined. It is often used when signs and symptoms do not conform to traditional anxiety diagnoses. Patients treated with SLO compared with placebo for subsyndromal anxiety disorder (n = 216) had significant overall improvements in HAMA (Table) and PSQI scores ($P = .002$), with perceived sleep latency ($P = .034$), sleep duration ($P = .001$), and sleep quality ($P = .003$) most improved.[51] In patients with anxiety-related restlessness and disturbed sleep (n = 170), there was no significant improvement in PSQI scores observed ($P = .091$), despite significant

reductions in HAMA scores (Table).50 Baseline PSQI scores were similar in patients between the two studies; thus, it appears that observed benefits on sleep were limited to patients with subsyndromal anxiety disorder. Although further studies are required to fully characterize SLO's effect on sleep architecture in different patient populations, PSQI and HAMA scores along with reported adverse effects suggest that SLO has an anxiolytic effect while lacking sedative or hypnotic properties.

Two other studies52,54 used active comparators and studied patients with GAD. The first study54 (n = 77) compared a single daily dose of lorazepam 0.5 mg to SLO 80 mg and found SLO to be noninferior. Although 0.5 mg of lorazepam may be an adequate dose for some patients, it may be subtherapeutic in others. The second and largest study to date52 (n = 536) featured both an active (paroxetine) and placebo control and compared them to SLO at both 80- and 160-mg daily dosages. The study found SLO in doses of 80 or 160 mg (administered as 80 mg orally twice a day) to be better than placebo in reducing HAMA scores, whereas the comparator paroxetine 20 mg did not separate significantly from placebo (Table). Paroxetine was administered in a fixed dose of 20 mg without titration, and although this may be a sufficient dose for some patients, others require higher doses to achieve response.55 Patients were monitored for the week after discontinuation of the study period for withdrawal symptoms, which were not observed in participants randomized to SLO. Additional secondary outcomes, including patient self-rating SF-36 Health Survey Questionnaire and clinician-rated Clinical Global Impressions scale, were assessed in both studies. SLO and paroxetine showed improvement over placebo, whereas positive comparable results were seen between SLO and lorazepam with GAD for both the SF-36 and Clinical Global Impressions.

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Discussion

Available trials support the short-term efficacy of the standardized lavender oil extract SLO in the treatment of anxiety disorders, including subsyndromal anxiety disorder (anxiety not otherwise specified), GAD, restlessness and agitation with disturbed sleep, and Mixed Anxiety and Depressive Disorder. Many treatment guidelines in anxiety disorders predate the publication of most of the randomized controlled trials featured in the Table. The British Association for Psychopharmacology (2014) and National Institute for Health and Clinical Excellence (2011) guidelines for GAD acknowledge evidence for SLO based on the single trial they examined[54]; however, sufficient data to make a definitive recommendation for use were not available at that time.[7,56]

The SLO appears to have a calming effect without producing sedation, which is advantageous compared with benzodiazepines or pregabalin. SLO also lacks a withdrawal syndrome and is not thought to have abuse potential.[52] Pharmacokinetic drug interaction potential appears minimal, and adverse effects observed in studies were mild. Onset of efficacy occurs within 2 weeks in patients who respond, in contrast to the 4 to 6 weeks it takes for monoamine reuptake–inhibiting antidepressants to have a therapeutic effect. Additionally, monoamine reuptake–inhibiting antidepressants often produce transient side effects upon initiation, including increased anxiety, often necessitating a short course of benzodiazepines for effective management.

There are many unanswered questions regarding the use of LEO in the treatment of anxiety, as well as limitations to the current body of evidence. Essential oil of lavender lacks evidence in many types of anxiety, such as panic and phobic disorders. Moreover, with the exception of GAD, the anxiety-related disorders studied tended to be nonspecific diagnoses given in the context of prominent symptoms that lacked criteria for a better defined anxiety disorder. Long-term safety studies are lacking, which is concerning, given that anxiety

disorders may be chronic conditions and LEO has displayed cytotoxic properties.[44] Given the variability in LEO preparations, it is also unclear if results observed in trials using SLO are reproducible using LEO from other sources or if constituents that are less well characterized are playing an important role in the oil's effect. Trials conducted have used SLO as monotherapy, so it is unknown if it is appropriate or effective to use adjunctively with traditional anxiolytic medications. When active comparators were used, doses were fixed and potentially subtherapeutic. All trials of SLO have been conducted in Germany and include mostly middle-aged white women, which reduces the ability to generalize results to other populations, such as children, adolescents, the elderly, or other ethnic groups. Psychiatric comorbidity is common with anxiety disorders, although many were excluded from clinical trials, which lowers the external validity of observed findings. Eructation (belching) was a commonly reported side effect in clinical trials, raising the question as to whether blinding may be compromised because patients could potentially taste lavender oil upon eructation.

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Conclusions

The SLO product exhibits many desirable properties of an anxiolytic agent, including a calming effect without sedation, as well as a lack of dependence, tolerance, or withdrawal. SLO has a relatively benign side effect profile in short-term studies, and its onset of efficacy is more rapid than current first-line agents. Evidence from multiple high-quality randomized trials suggests a role for SLO in the treatment of anxiety disorders. The favorable safety and efficacy profile of SLO makes it a reasonable alternative to consider in patients with anxiety disorders. Clinicians should exercise caution given limitations of the current evidence base and lack of Food and Drug Administration endorsement in the management of anxiety disorders.

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Footnotes

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Lavender and the Nervous System

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Abstract

Lavender is traditionally alleged to have a variety of therapeutic and curative properties, ranging from inducing relaxation to treating parasitic infections, burns, insect bites, and spasm. There is growing evidence suggesting that lavender oil may be an effective medicament in treatment of several neurological disorders. Several animal and human investigations suggest anxiolytic, mood stabilizer, sedative, analgesic, and anticonvulsive and neuroprotective properties for lavender. These studies raised the possibility of revival of lavender therapeutic efficacy in neurological disorders. In this paper, a survey on current experimental and clinical state of knowledge about the effect of lavender on the nervous system is given.

Go to:

1. Introduction

The genus *Lavandula* is native to the lands surrounding the Mediterranean Sea and southern Europe through northern and eastern Africa and Middle Eastern countries to southwest Asia and southeast India. It includes more than 30 species, dozens of subspecies, and hundreds of hybrids and selected cultivars.

The different varieties of this plant range in height from 9 inches to 3 feet, although some may grow taller with age. Lavender are divided into four main categories: *L. angustifolia*, commonly known as English Lavender, is a frost hardy species that has many pretty cultivars, habit, and blossom color (formerly known as *L. vera* or *L. officinalis*); *L. stoechas* is a large plant with greenish-grey foliage and late blooming with a very strong odor (sometimes known as French lavender); *L. latifolia*, a Mediterranean grass-like lavender; and *L. intermedia*, which is a sterile cross between *L. latifolia* and *L. angustifolia*. The various lavenders have similar ethnobotanical properties and major chemical constituents [1].

The main constituents of lavender are linalool, linalyl acetate, 1,8-cineole *B*-ocimene, terpinen-4-ol, and camphor. However, the relative level of each of these constituents varies in different species [1, 2]. Lavender oil, obtained from the flowers of *Lavandula angustifolia* (Family: Lamiaceae) by steam distillation, is chiefly composed of linalyl acetate (3,7-dimethyl-1,6-octadien-3yl acetate), linalool (3,7-dimethylocta-1,6-dien-3-ol), lavandulol, 1,8-cineole, lavandulyl acetate, and camphor. Whole lavender oil and its major components linalool and linalyl acetate are used in aromatherapy. The major components of lavender oil were identified as 51% linalyl acetate and 35% linalool measured by gas chromatography and gas chromatography-linked Fourier Transform Infrared analysis [1–3].

Most commonly lavender is recommended for oral administration. However, it is also being employed in aromatherapy (inhalation of lavender; [4, 5]), aromatherapy massage, dripping oil [6], and bathing [7]. Unlike many other essential oils used in aromatherapy, lavender oil is often applied undiluted to the skin. The study of Jager et al. [8] suggested that essential oils and their components are rapidly absorbed through the skin. Linalool and linalyl acetate were shown to be rapidly detected in plasma after topical application with massage, reaching peak levels after approximately 19 min [8]. At least since medieval periods, lavender has been a source of drugs as well as perfumes, soaps, flavorings, and crafts. Lavender has a long history of medicinal use and is suggested to possess anticonvulsant, antidepressive, anxiolytic, sedative, and calming properties [1, 9–12]. Lavender also prescribed by some medieval physicians such as Ebn-e-sina and Razi for treatment of epilepsy and migraine attacks. Furthermore, lavender is considered beneficial in treatment of pain and tremor [9–12].

In recent years, several animal and human investigations have indeed evaluated traditional medical remedies of lavender using modern scientific methods. These studies raised the possibility of revival of lavender therapeutic efficacy in neurological disorders on the basis of evidence-based medicine [12, 13].

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2. Animal Studies

Several animal experiments suggest anxiolytic, sedative, analgesic, and anticonvulsive and neuroprotective properties for lavender [14]. It was shown that lavender possesses an anticonflict effect in mice [15]. Continuous exposures to lavender essential oils for 7 days significantly inhibited anxiety- and depression-like behaviors tested by elevated plus-maze and forced swimming tests in rats [16]. Lavender oil produced significant antianxiety effects in the Geller

conflict and the Vogel conflict tests in mice. Linalool, a major constituent of lavender oil, produced significant anticonflict effects in the Geller and Vogel tests; findings that were similar to those of lavender oil [17]. Effects of lavender oil were compared with chlordiazepoxide, as a reference anxiolytic, on open-field behavior in rats. Lavender oil exhibited antianxiety properties similar to those of chlordiazepoxide [18]. Anxiolytic effect of lavender was also compared with diazepam in elevated plus-maze test in the Mongolian gerbil. Exposure to lavender odor showed an anxiolytic profile similar to diazepam in female gerbils [19]. Investigation of the effects of inhaled linalool on anxiety, aggressiveness, and social interaction in mice showed anxiolytic properties in the light/dark test, increased social interaction, and decreased aggressive behavior [20].

Local anesthetic effect of lavender and its constituents (linalool and linalyl acetate) is reported in both in vivo and in vitro animal experiments [21]. In the rabbit conjunctival reflex test, treatment with a solution of lavender essential oil as well as with linalyl acetate or linalool induced a dose-dependent enhancement in the number of stimuli necessary to provoke the reflex [21]. The methanolic extract of lavender (200–600 mg/kg) dose-dependently produced sedative effects in mice. This was indicated by the relatively longer time for the reestablishment and number of head dips during the traction and hole-board tests [22]. To evaluate the sedative effects of lavender, the immobility of overagitated mice induced by caffeine was ascertained after the inhalation of lavender. Lavender odor significantly increased the immobile state in mice treated with caffeine [23]. Exposure of mice to lavender odor in a dark cage resulted in depression of motor activity, whilst the plasma levels of linalool rose in proportion to the length of exposure [24]. The intraplantar injection of capsaicin produced an intense and short-lived licking/biting response in mice. The capsaicin-induced nociceptive response was reduced significantly by intraplantar injection of lavender and linalool [25]. Either oral administration or inhalation of lavender essential oil significantly

reduced the chemical and thermal pain without evidence of central adverse effects in adult mice. Opioidergic neurotransmission seems to be involved in lavender-induced analgesia since only naloxone pretreatment prevents its effect in writhing test. Cholinergic neurotransmitter system also appears to play a role in lavender analgesia. The blockade of muscarinic and nicotinic receptors prevented analgesic effects of lavender [26].

Exposure to lavender effectively improved spatial memory deficits induced by dysfunction of the cholinergic system [27]. Administration of lavender in animal model of Alzheimer's disease (rat model established by intracerebroventricular injection of Aβ1) effectively reversed spatial learning deficits [28]. Repeated application of lavender in mice demonstrated a more rapid sleep onset with longer duration of sleep [29]. Anticonvulsant effect for hydroalcoholic extract of lavender was reported against chemoconvulsant-induced seizures in male mice. Lavender inhibited the onset, shortened the duration, and reduced the intensity of seizure attacks [30]. Anticonvulsant effects of lavender together with diminution in spontaneous activity, when combined with other narcotics, have been reported [31, 32]. Inhalation of lavender was also noted to inhibit convulsion induced by pentylenetetrazol, nicotine, or electroshock in mice [33]. Linalool, one of the major components of lavender oil, has been shown to inhibit the convulsion induced by pentylenetetrazol and transcorneal electroshock in different animal models [34, 35], an effect that may induce via a direct interaction with the glutamatergic NMDA subreceptor as well as $GABA_A$ receptors [36]. The neuroprotective effect of lavender oil on cerebral ischemia/reperfusion injury was investigated in mice. Focal cerebral ischemia was induced by the intraluminal occlusion. An aqueous extract of lavender has been shown to diminish glutamate-induced neurotoxicity in rat pups cerebellar granular cell culture [37]. Lavender oil significantly decreased neurological deficit scores, infarct size, and the levels of mitochondria-generated reactive oxygen species and attenuated

neuronal damage in focal cerebral ischemia induced by the intraluminal occlusion in mice [38].

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3. Mechanisms of Action of Lavender in the Nervous System

Several investigations were performed to clarify the mechanism of action of lavender in neuronal tissues. Lavender inhibited lipopolysaccharide-induced inflammatory reaction in human monocyte THP-1 cells effect, which might be associated with the expression of HSP70 [39]. Antioxidant and relatively weak cholinergic inhibition was reported for lavender [38, 40] and linalool [41–43]. Linalool inhibited acetylcholine release and alters ion channel function at the neuromuscular junction [44]. These findings indicate that several targets relevant to treatment of Alzheimer's disease; anticholinergic, neuroprotective, and antioxidant activities could be found in lavender. The neuroprotective effect of lavender oil against cerebral ischemia/reperfusion injury is suggested to be attributed to its antioxidant effects [38]. Evaluation of the effects of lavender oil on motor activity and its relationship to dopaminergic neurotransmission revealed that intraperitoneal application of lavender significantly increased rotarod activity and enhanced dopamine receptors subtype D_3 in the olfactory bulbs of mice [45]. Lavender oil is also suggested to modulate GABAergic neurotransmission, especially on $GABA_A$ receptors, and enhance inhibitory tone of the nervous system [29, 36, 46]. Cholinergic system is suggested to play a role in lavender analgesic, antianxiety, antidepression, and anticonvulsant effects of lavender [16, 26, 33].

Fos is a nuclear transcription factor protein encoded by an immediate early gene c-fos, and it is an early marker of neuronal activation. It serves as a transcriptional factor controlling the expression of genes expected to be involved in effective adaptation to certain situations. Lavender oil reduced c-fos expression in paraventricular nucleus of

the hypothalamus and dorsomedial hypothalamic nucleus [18]. Lavender oil inhibited dose-dependently the histamine release and anti-DNP IgE-induced tumor necrosis factor-alpha secretion from peritoneal mast cells in mice [47]. It has been shown that lavender oil inhibited the sympathetic nerves innervating the white and brown adipose tissues and adrenal gland and excites the parasympathetic gastric nerve [48, 49]. Odor of lavender oil, and especially its component linalool, affects autonomic nerves probably through a histaminergic response, decreases lipolysis and heat production (energy consumption), and increases appetite and body weight in rats [50]. Lavender may inhibit the sympathetic nerve activity and lipolysis through activation of H_3-receptors. The hypothalamic suprachiasmatic nucleus and histamine neurons are involved in the lipolytic responses to the lavender oil, and tyrosine phosphorylation of BIT (a brain immunoglobulin-like molecule with tyrosine-based activation motifs, a member of the signal-regulator protein family) is implicated in the relevant signaling pathways [50].

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4. Human Studies

Although there is considerable debate about whether lavender species have a significant clinical potential either alone or as additives to other substances, many human studies support its effectiveness in different neurological and psychological disorders. Lavender was used predominantly in oral administration, aromatherapy, or massage in several clinical studies, and many benefits were claimed for use in such a manner. In addition to psychological effects, aromatherapy is thought to be therapeutically effective due to physiological effects of the inhaled volatile compounds. It is believed that inhaled lavender act via the limbic system, particularly the amygdala and hippocampus [1]. Linalool and linalyl acetate are rapidly absorbed through the skin after topical application with massage and are thought to be able to cause central nervous system depression [8].

4.1. Anxiety, Depression, and Lavender

Lavender was used in the treatment of anxiety disorders and related conditions. Three clinical trials were identified which investigated the efficacy of oral lavender oil preparation (silexan; an essential oil produced from lavender flowers by steam distillation), administered once daily at a dose of 80 mg/day, in subsyndromal (mixed) anxiety disorder and generalized anxiety disorder as well as in restlessness and agitation. Anxiolytic effect of lavender was superior to placebo in 221 patients suffering from anxiety disorder. In addition, lavender improved associated symptoms such as restlessness, disturbed sleep, and somatic complaints and had a beneficial influence on general well-being and quality of life [51, 52]. In line with this study, the efficacy of a 6-week-intake of oral lavender oil preparation (Silexan, 80 mg/day), compared to lorazepam, was investigated in adults with generalized anxiety disorder. This study indicates that lavender effectively ameliorates generalized anxiety comparable to 0.5 mg/daily lorazepam [53]. Alleviation of anxiety and mood improvement were reported in thirty-six patients admitted to an intensive care unit, who received lavender oil (diluted to 1% concentration) aromatherapy [54]. The same results were reported for fourteen female patients who were being treated with chronic hemodialysis [55]. A survey in a long-stay neurology in-patient department showed increased mood scores and reduced psychological distress following aromatherapy with lavender accompanied with tea tree and rosemary [56]. An investigation on the effect of lavender aromatherapy (diluted to 2% concentration) on anxiety and depression in the high risk postpartum woman showed a significant improvement of the Edinburgh Postnatal Depression Scale and Generalized Anxiety Disorder Scale after four consecutive weeks of administration of lavender [57]. Lavender odor reduced anxiety in dental patients; however, it has no effect on dental anxiety surrounding thoughts of future dental visits [58, 59]. Testing visual analog scales to assess anxiety, it is suggested that lavender is a simple, low-risk, cost-effective intervention with the potential to

improve preoperative anxiety [60]. Orally administered lavender capsules contained 100 or 200 μL of organic *Lavandula angustifolia* oil were tested on responses to anxiety-provoking film clips. In this study, evaluation of State Trait Anxiety Inventory, mood, positive and negative affect scale, heart rate, and galvanic skin response as well as heart rate variation after administration of lavender suggests that lavender has anxiolytic effects in humans suffering from low anxiety, but these effects may not extend to conditions of severe anxiety [61]. A clinical investigation points to antidepressive effect of lavender. Adjuvant therapy of lavender tincture (1 : 5 in 50% alcohol; 60 drops/day) and imipramine (100 mg/daily) in treatment of forty-eight adult outpatients suffering from mild-to-moderate depression led to a better and earlier improvement. Anticholinergic side effects of imipramine, such as dry mouth and urinary retention, were observed less often when lavender administered with impramine. These results suggest that lavender is an effective adjuvant therapy in combination with imipramine, resulting in a superior and quicker improvement in depressive symptoms [62].

4.2. Neuroimaging and Lavender

Evaluation of brain regional metabolic activity with positron emission tomography in ten healthy women after the lavender odor stimulus demonstrated neuronal enhancement in the orbitofrontal, posterior cingulate gyrus, brainstem, thalamus, and cerebellum and reduction of activity in the pre/post-central gyrus and frontal eye field. These findings indicate that lavender aromatherapy in addition to relaxation effect may enhance arousal level in some subjects [63]. Using functional magnetic resonance imaging (fMRI), significant activation in major olfactory brain structures, including the primary olfactory cortex, entorhinal cortex, hippocampus and parahippocampal cortex, thalamus, hypothalamus, orbitofrontal cortex, and insular cortex and its extension into the inferior lateral frontal region was reported in nineteen healthy participants after application of 10% lavender diluted in dipropylene glycol [64]. Cortical perfusion increment after

sensorial stimulation with lavender was evaluated by single photon emission computed tomography in ten healthy adults. A significant activation was observed in gyrus rectus, orbitofrontal cortex, and superior temporal cortical areas. A slight perfusion increase also existed in middle temporal and parieto-occipital regions [65]. Lavender odor was delivered via the orthonasal (odor perceived through the nose) and retronasal (odor perceived through the mouth) routes and brain response was measured with fMRI in 20 subjects. In addition to the activation at the base of the central sulcus by lavender, retronasal stimulation with odor resulted in a significant peak in the ventral insula compare to orthonasal application. In contrast, orthonasal application yielded a peak in the right caudate nucleus that approached significance in comparison to retronasal way [66].

4.3. Electroencephalography (EEG) and Lavender

It has been suggested that some neurological disorders with significant EEG changes, such as epilepsy, may be benefited by aromatherapy [10, 11]. Lavender affects human EEG pattern accompanied with its anxiolytic effect. It is reported that inhalation of lavender (diluted to 10% concentration) for 3 minutes increases alpha power of EEG as decreases anxiety and brings the subject to a better mood in 40 healthy adults [67]. Increases in theta (4–8 Hz) and alpha (8–13 Hz) wave activity may cause a range of general relaxation effects and can be induced by chemical and nonchemical techniques [68]. It has been shown that during inhalation with lavender (diluted to 10% concentration) in 20 participants, the power of theta and alpha wave activities were significantly increased in all brain regions. This study found relaxing effects with increases of alpha wave activities after administering lavender; indicating the EEG evidence of relaxation by lavender aromatherapy [69]. Furthermore, lavender aromatherapy is reported to produces EEG patterns characteristics of subjects' feeling comfortable [70]. Lavender oil administered in an aroma stream shows modest efficacy in the treatment of agitated behavior in patients with severe dementia [71].

Resting frontal EEG asymmetry is suggested to be a predictor of symptom change and end-state functioning in patients with social anxiety disorder who undergo efficacious psychological treatment [72]. Evaluation of frontal EEG asymmetry shifting in thirty-nine adult participants and twenty-seven full-term newborns revealed greater relative left frontal EEG activation (associated with greater approach behavior and less depressed affect) after aromatherapy with lavender. Further studies in these volunteers indicate that lavender may induce left frontal EEG shifting in adults and infants, who show greater baselines relative to right frontal EEG activation. It is suggested that both infants and adults with greater relative right frontal EEG activation at baseline may be more affected by lavender application [73].

4.4. Sleep and Lavender

Lavender has been suggested as an excellent natural remedy to treat insomnia and improve the sleep quality. Single-blind randomized studies investigated the effectiveness of lavender odor on quality of sleep showed that lavender improved the mean scores of sleep quality in fifteen healthy students [74], in sixty-four ischemic heart disease patients [75], and in thirty-four midlife women with insomnia [76]. Ten individuals with insomnia, verified by a score of 5 or more on the Pittsburgh Sleep Quality Index (PSQI), were treated with lavender odor. Six to eight drops of lavender oil added each night to the cartridge improved the PSQI score by −2.5 points. More notable improvements were seen in females and younger participants. Milder insomnia also improved more than severe ones [77]. Oral lavender oil preparation (80 mg/day) showed a significant beneficial influence on quality and duration of sleep and improved general mental and physical health without causing any unwanted sedative or other drug specific effects in 221 patients suffering from subsyndromal (mixed) anxiety disorder [52]. A mixture of essential oils including lavender, basil, juniper, and sweet marjoram is shown to reduce sleep disturbance and improve overall well-being in older patients [78]. In a

clinical study on four benzodiazepine dependent geriatric patients, there was a significant decrease in sleep duration by stopping benzodiazepine treatment, which was restored to previous levels by substitution of aromatherapy with lavender oil. This study suggested that ambient lavender oil might be used as a temporary relief from continued medication for insomnia and reduces the side-effects of these drugs [79]. In a study on thirty-one hospitalized patients, administration of lavender odor showed a trend towards an improved quality of daytime wakefulness and more sustained sleep at night [80]. In contrary to these data, it should be noted that the use of aromatherapy massage with lavender oil has no beneficial effect on the sleep patterns of children with autism attending a residential school. It was suggested that this therapy may show greater effects in the home environment or with longer-term interventions [81].

4.5. Pain and Lavender

Lavender reported to be useful in the treatment of acute as well as chronic or intractable pain [82]. It has been shown that foot massage using lavender essential oil in 100 ICU patients of whom 50% were receiving artificial ventilation was effective in lowering blood pressure, heart rate, respiratory rate, wakefulness, and pain [83]. Treatment of recurrent aphthous ulceration with lavender oil in 115 patients revealed a significant pain relief mostly from the first dose, ulcer size reduction, increased rate of mucosal repair, and healing within three days of treatment compared to baseline and placebo groups [84]. Stress level, the bispectral index (a promising parameter for monitoring sedation), and pain intensity of needle insertion were significantly reduced after receiving oxygen with a face mask coated with lavender oil for five minutes compared with the control in thirty volunteers [85]. Aromatic oil massage with essential oils blended with lavender, clary sage, and marjoram in a 2 : 1 : 1 ratio in forty-eight outpatients with primary dysmenorrhea alleviated the pain and reduced the duration of dysmenorrhea [86]. Aromatherapy by using lavender essence was also reported as a successful and safe

complementary therapy in reduction of pain after the cesarean section in 200 term pregnant women [87] and after episiotomy in 60 primiparous women [88] as well as in perineal discomfort following normal childbirth in 635 women [89, 90]. It has been shown that lavender aromatherapy through an oxygen face mask with two drops of 2% lavender oil can be used to reduce the demand for opioids in twenty-five patients after immediate postoperative period of breast biopsy surgery [91] and for other analgesics in fifty-four patients undergoing laparoscopic adjustable gastric banding [92]. In contrast to these observations, the aroma of essential oil of lavender ease anxiety but not perception of pain during elective cosmetic facial injections of botulinum toxin for the correction of glabellar wrinkle [93]. A course of eight-session manual acupressure with lavender oil (3% lavender oil; used as the massage lubricant) over a three-week period in patients with nonspecific subacute neck pain (32 patients) or low back pain (61 patients) significantly alleviated the neck and back pain and improved movements of the cervical and lumbar spine [94, 95]. Inhalation of lavender essential oil is suggested to be an effective and safe treatment modality in acute management of migraine headaches. Forty-seven patients suffering from migraine attacks reported significant reduction of pain severity and associated symptoms after fifteen minutes inhalation of lavender oil (2-3 drops of the lavender essential oil rubbed onto their upper lip) in the early stages of the attacks [5]. Aromatherapy massage with lavender accompanied with rose geranium, rose, and jasmine in almond and primrose oils once a week for 8 weeks is reported as an effective treatment of menopausal symptoms such as hot flushes, depression, and pain in climacteric women [96].

4.6. Cognition and Lavender

The use of aromas to modulate affect and mood has been reported by several ancient and medieval physicians [9–12]. The positive effects of different medicinal plants as cognition enhancers have been reported [97]. To assess the olfactory impact of the essential oils of lavender on

cognitive performance and mood in healthy volunteers, the Cognitive Drug Research computerized cognitive assessment battery was performed in 144 participants. Analysis of performance revealed that lavender odor (four drops of oil were applied to a diffuser pad) produced a significant decrement in performance of working memory as well as impaired reaction times for both memory and attention. In addition, a significant effect was found for lavender compared to controls for degree of contentedness, indicating that lavender is capable of elevating mood, or at least maintaining good mood during the completion of a challenging test battery under laboratory conditions [98]. There is an improvement of emotional state in the work environment following the use of the lavender oil burners. Using lavender oil in burners for a 3-month period, nearly 90% of respondents (a total of 66 subjects) believed that there had been an improvement in the work environment following the use of lavender oil [99]. Aromatherapy consisted of the use of rosemary and lemon essential oils in the morning, and lavender and orange in the evening showed significant improvement in personal orientation related to cognitive function in 28 elderly patients suffering from different forms of dementia [100]. It has been shown that unconscious perception of lavender odor can significantly affect the rate of errors made in the mathematical and letter counting tests. In the presence of the odor of lavender, 108 subjects made fewer errors than in the presence of no odor or the odor of jasmine [101]. By comparison, it has been reported lavender to impair arithmetic reasoning, but not memory, when compared to cloves, with no concomitant effect on mood for either odor [102]. Application of oral lavender (80 mg/day) for six weeks in fifty patients suffering from neurasthenia or post-traumatic stress disorder showed significant improvements of their general mental health status and quality of life [103].

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5. Safety

Although sufficient evidence exists to recommend lavender for short-term treatment of some neurological disorders, long-term trials and observational studies are needed to establish the safety of long-term use as well as overall efficacy in the context of treatment and management of these diseases. The available data suggests that short-term therapy with lavender is relatively safe. However, there are some reports of adverse effects after application of lavender. Gynecomastia coincided with the topical application of products, which contained lavender and tea tree oils was reported in three boys aged between 7 to 10 years. Gynecomastia resolved in all patients shortly after discontinuation of products containing these oils. Furthermore, studies in human cell lines indicated that the lavender oil had estrogenic and antiandrogenic activities [104]. Lavender should be also used cautiously or avoided in patients with known allergy to lavender [105, 106]. In the oral lavender trials, Kasper et al. [52] reported slightly more adverse events in the lavender group than the placebo group; the most frequently reported adverse effects were related to infections and infestations, followed by gastrointestinal disorders and nervous system disorders. Woelk and Schläfke [107] reported slightly more adverse events in the lavender group than the lorazepam group but again none were described as serious. Gastrointestinal adverse events, such as nausea and dyspepsia, after receiving silexan were reported [107]. Ingestion should be avoided during pregnancy (due to emmenagogue effects) [108] and breastfeeding. Lavender oil has no potential for drug abuse [109].

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6. Critical Overview and Conclusion

A recent increase in the popularity of alternative medicine and natural products has renewed interest in lavender and their essential oils as potential natural remedies [2]. This review may be useful to increase our knowledge of lavender pharmacological effects and improve our future experimental and clinical research plans. Although it is shown

that lavender may have a significant clinical potential either in their own right or as adjuvant therapy in different disorders, however, due to some issues, such as methodological inadequacies, small sample sizes, short duration of lavender application, lack of information regarding dose rationale, variation between efficacy and effectiveness trials, variability of administration methods, the absence of a placebo comparator, or lack of control groups more standard experiments and researches are needed to confirm the beneficial effect of lavender in the neurological disorders [109]. Methodological and oil identification problems have also hampered the evaluation of the therapeutic significance of some of the research on lavender. The dried lavender flowers used in some trials were sourced from a local herb store (i.e., [62]). Although taxonomic identification was confirmed in these studies, without quantification of key constituents the quality of the herbal product may be questionable [110]. Although some studies defined the contents of lavender, it is essential that all future clinical studies specify the exact derivation of the oils used in the study and, preferably, include a profile of the liquid or the percentage composition of the major constituents. In addition, several factors, such as temperature, skin type and quality, and the size of area being treated, which may affect the level and rate of lavender absorption after massage or aromatherapy, were not considered in several investigations. Many discreet compounds in lavender oil have shown a myriad of potential therapeutic effects, and researchers continue to seek novel treatments to different ailments [2].

Only few clinical investigations on lavender are available using diverse administration methods (i.e., oral, aromatherapy, and as a massage oil). The evidence for oral lavender is promising; however, until independent studies emerge with long-term follow-up data, it remains inconclusive [109]. The use of more widely used forms of lavender administrations (aromatherapy, inhalation, massage, etc.) is not currently supported by good evidence of efficacy. Future clinical trials, well-reported and adopting rigorous standard methodology, in

combination with experimental pharmacological research, would help to clarify the therapeutic value of lavender for neurological and psychological disorders [109, 110].

The apparently low reporting of adverse reactions could imply tolerability and safety [110]. However, most studies failed to provide details which may have masked these and the studies only involved small numbers of participants. It is crucial to get good tolerability and safety data for all modes of lavender application. Thus longer-term follow ups would be required especially for oral lavender before it is recommended for treatment of neurological and/or psychological disorders.

Go to:

Authors' Contribution

P. H. Koulivand and M. K. Ghadiri contributed equally to this paper.

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Review

Effects of lavender on anxiety: A systematic review and meta-analysis

Abstract

Background

Anxiety is one of the uprising psychiatric disorders of the last decades and lavender administration has been traditionally suggested as a possible treatment. The objective of this review is to assess the efficacy of lavender, in any form and way of administration, on anxiety and anxiety-related conditions.

Methods

The PRISMA guidelines were followed. Retrieved data were qualitatively and quantitatively synthesized. Randomized Controlled Trials (RCTs) and Non-Randomized Studies (NRSs) which investigated the efficacy of lavender, in any form and way of administration, on patients with anxiety, involved in anxiety-inducing settings or undergoing anxiety-inducing activities, compared to any type of control, without language restrictions, were identified through electronic database searches. Medline via PubMed, Scopus, Web of Science, Cochrane Library, EMBASE, and Google Scholar were systematically searched. All databases were screened up to November 2018. Risk of bias was assessed with the Cochrane risk-of-bias tool and the following domains were considered: randomization, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases.

Results

65 RCTs (7993 participants) and 25 NRSs (1200 participants) were included in the qualitative synthesis and 37 RCTs (3964 participants) were included in the quantitative synthesis. Overall, the qualitative synthesis indicated that 54 RCTs and 17 NRSs reported at least a significant result in favor of lavender use for anxiety. The quantitative synthesis showed that lavender inhalation can significantly reduce anxiety levels measured with any validated scale (Hedges' g = −0.73 [95% CI −1.00 to −0.46], $p < 0.00001$, 1682 participants), as well as state anxiety (Spielberger's state-trait anxiety inventory (STAI)-State mean difference = −5.99 [95% CI −9.39 to −2.59], $p < 0.001$, 901 participants) and trait anxiety (STAI-Trait mean difference = −8.14 [95% CI −14.44 to −1.84], $p < 0.05$, 196 participants). Lavender inhalation did not show a significant effect in reducing systolic blood pressure as a physiological parameter of anxiety. A significant effect in diminishing anxiety

levels was also found in favor of the use of oral Silexan® 80 mg/die for at least 6 weeks (Hamilton Anxiety Scale mean difference = −2.90 [95% CI −4.86 to −0.95], $p = 0.004$, 1173 participants; Zung Self-rating Anxiety Scale mean difference = −2.62 [95% CI −4.84 to −0.39], $p < 0.05$, 451 participants) or of the administration of massage with lavender oil (Hedges' g = −0.66 [95% CI −0.97 to −0.35], $p < 0.0001$, 448 participants).

Discussion

The most important limitation of this review is the low average quality of available studies on the topic. The majority of included RCTs were characterized by a high overall risk of bias. Another limitation regards the heterogeneity of study designs, especially with regard to non-oral ways of administration. Overall, oral administration of lavender essential oil proves to be effective in the treatment of anxiety, whereas for inhalation there is only an indication of an effect of reasonable size, due to the heterogeneity of available studies. Lavender essential oil administered through massage appears effective, but available studies are not sufficient to determine whether the benefit is due to a specific effect of lavender. Further high-quality RCTs with more homogeneous study designs are needed to confirm these findings. Available information outlines a safe profile for lavender-based interventions, although more attention should be paid to the collection and reporting of safety data in future studies. Considering these findings, since treatments with lavender essential oil generally seem safe, and, in the case of inhalation, also simple and inexpensive, they are a therapeutic option which may be considered in some clinical contexts.

Other

The present systematic review was not funded and was registered in PROSPERO under the following number: CRD42019130126.

Introduction

Anxiety is one of the uprising psychiatric disorders of the last decades (Bandelow and Michaelis, 2015). Anxiety disorders are thought to have a worldwide prevalence of up to 15% in the general

population (Baxter et al., 2013), and are twice as common in women as in men (Bandelow and Michaelis, 2015). According to the DSM-V, anxiety disorders are frequent non-psychotic mental disorders, comprising Generalized Anxiety Disorder (GAD), phobias, panic attacks, obsessive-compulsive disorder, and other disturbs belonging to the broad category of “anxiety disorders without other specification” (American Psychiatric Association, 2013). In general, anxiety disorders share features of excessive fear and anxiety, as well as of related behavioral disturbances. While fear is the emotional response to an imminent threat, characterized by an acute autonomic system activation, anxiety is better described as the “anticipation of a future threat”. Anxiety conditions are often assessed through the use of questionnaires administered to patients, however, the measurement of psychophysiological parameters (e.g. respiratory rate, heart rate and its variability, as well as systolic and diastolic blood pressure) are used as well.

In clinical practice, first-line treatments for anxiety are lifestyle changes, cognitive-behavioral therapy (CBT), selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs). Benzodiazepines are also very effective anxiolytic drugs, but their use can lead to adverse effects like cognitive impairment, falls, sedation, as well as dependence, tolerance, rebound anxiety, and discontinuation syndrome, so they are not considered a good first-line treatment option (Andrews et al., 2018).

Traditionally, lavender as an herbal remedy has been associated with anxiolytic properties.

Lavender is a plant from the *Lamiaceae* family, and many species with different chemical characteristics exist, including *Lavandula angustifolia* (also called *L. vera* or *L. officinalis), L. stoechas, L. latifolia,* and *Lavandula x intermedia* (a cross between *L. latifolia* and *L. angustifolia*). Although different from a botanical point of view, the above mentioned lavender species share similar major chemical constituents and properties (Cavanagh and Wilkinson, 2002). In general, lavender is chemically made of over 100 constituents, including terpenes like linalool, limonene, triterpenes, linalyl acetate, alcohols like perillyl alcohol, ketones like camphor, polyphenols like tannins, but also coumarins, cineole, and flavonoids, at different

percentages (Basch et al., 2004). The key constituents of *L. angustifolia,* which is the most commonly used species of lavender, are linalyl acetate and linalool, and, although linalyl acetate has the greater proportion, linalool is considered the primary active constituent. Both components, though, are responsible for the pharmacological effects of lavender, including its supposed calming and sedative activity (Basch et al., 2004).

The location of cultivations and characteristics of the soil are essential to determine the specific composition of lavender extracts (Adam, 2006). There are many methods to extract essential oils from lavender: hydro-distillation, steam distillation, solvent extraction, and supercritical CO_2 extraction. Minor methods, such as exsiccation of lavender flowers, and hydrosols, are usually employed for the production of handmade cosmetics. Lavender is often administered in the form of essential oil distilled from lavender flowers, while other formulations include dried flowers or hydrosols (Adam, 2006). Lavender products can be administered orally, topically, or through inhalation (Basch et al., 2004). A particular way to administer lavender is represented by Silexan®, which is a lavender standardized essential oil titrated in linalool and linalyl acetate, obtained from steam distillation of fresh *L. angustifolia Miller* flowers. In the production of Silexan®, particular attention is given to lavender cultivation, harvesting, as well as to oil extraction, in order to minimize the plant composition variability, and obtain a product with a high concentration of linalool and linalyl acetate (Kasper et al., 2010)**.** Silexan® is registered in Germany as an over-the-counter medicinal product and commercialized in the form of branded capsules, while, in other countries, it is marketed as a dietary supplement.

In in-vivo pharmacodynamic experiments, lavender showed sedative effects: when intraperitoneally administered to rats, it doubled the duration of anesthesia induced by hexobarbital sodium, and prolonged anesthesia caused by alcohol, whereas in male albino mice it reduced spontaneous locomotor activity (Escop, 2009). In two studies with female mice, after 60 min of inhalation, motility was reduced by 43% and 78% with essential oil, by 15% and 73% with linalool, and by 35% and 69% with linalyl acetate (Buchbauer et al., 1993, 1991). Interactions of lavender essential oil with numerous neuropharmacological targets, such as the ionotropic MAO-A, the SERT (serotonin transporter) and

ionotropic receptors (GABA-A and NMDA), were tested. In one study it was suggested that lavender essential oil can reversibly inhibit GABA-induced currents in a concentration-dependent manner (Huang et al., 2008). Potentiation effects of lavender essential oil and some of its constituents on GABA receptors were also reported in other research works (Aoshima and Hamamoto, 1999; Cavanagh and Wilkinson, 2002), and interactions of linalool with the glutamatergic system and the NMDA receptor were described by several authors too (Aprotosoaie et al., 2014; Elisabetsky et al., 1999, 1995; Schuwald et al., 2013; Silva Brum et al., 2001). The anxiolytic properties of lavender may be due to the fact that its main constituents can antagonize the NMDA-receptor and inhibit the SERT (López et al., 2017). This molecular affinity could explain the anti-agitation properties found for these products in animals. Lavender essential oil was also reported to inhibit tension-dependent calcium channels in murine synaptosomes, primary hippocampal neurons and specific cell lines (Schuwald et al., 2013). Another possible mechanism of action can be mediated by the 5HT-1A receptor in specific areas (hippocampus, anterior cingulate cortex, temporal gyrus, fusiform gyrus, insula), through a general reduction of its expression and binding potential (Baldinger et al., 2015). This effect would be in common with selective serotonin reuptake inhibitors (SSRIs), although the mechanism by which this effect is produced differs between the two (Baldinger et al., 2015; Kraus et al., 2014). However, lavender essential oil does not seem to alter gray matter volume as it occurs with SSRIs (Baldinger et al., 2015).

This has led researchers to study the administration of lavender-based products to treat anxiety, but clear evidence to support its use in clinical practice lacks to date. In fact, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) adopted a final monograph on the essential oil obtained from *L. angustifolia* Miller as a “traditional” herbal medicinal product with the following therapeutic indications: relief of mild symptoms of mental stress and exhaustion, sleep aid (Anonymous, 2018). However, to date, indications of this herbal remedy are exclusively based on tradition and long-standing use.

The aim of the present study is to systematically review existing scientific literature on the efficacy of lavender for anxiety and anxiety-related disorders in clinical settings, and to qualitatively and

quantitatively synthesize available data in order to outline its efficacy and possible uses in clinical practice.

Materials and methods

Protocol and registration

The PRISMA statement was followed for this systematic review and meta-analysis (Liberati et al., 2009). The protocol of the review was registered in PROSPERO under the following registration number: CRD42019130126.

Eligibility criteria

All types of study investigating therapeutic effects of lavender (any formulation) on patients with anxiety, either diagnosed with the DSM criteria (American Psychiatric Association, 2013) or involved in an anxiety-inducing setting or undergoing an anxiety-inducing activity, were included.
Clinical trials with human subjects were included, whereas experiments with animals or in vitro studies were excluded. Trials were excluded when the number of studied patients was unclear or unspecified.
Studies were included when intervention comprised the oral, topical (e.g. massage, baths), or inhalation (e.g. aromatherapy) routes of administration of lavender essential oil, lavender extracts, or other types of lavender-derived therapeutic products. All studies were included regardless of used lavender species. Studies were excluded when patients were exposed to a blend of lavender and other herbs of unclear composition, when the percentage of lavender in the blend was missing, or when lavender did not account for the majority of the blend composition.
All eligible trials were included regardless of the type of control (no intervention or placebo) or comparison (any intervention other than lavender administration) group.

Studies were included if anxiety and anxiety-related outcomes were assessed with at least one validated anxiety scale, like (but not limited to) the following ones: the Spielberger's State and Trait Anxiety Inventory (STAI), which can measure both state and trait anxiety (Spielberger, 1983); the Visual Analog Scale (VAS), a

10 mm scale used by patients to visually indicate the magnitude of their anxiety levels (Facco et al., 2011); the Profile of Moods Scale (POMS), employed to assess transient, distinct mood states including the “tension-anxiety” domain (Terry et al., 2003); the Hospital Anxiety and Depression Scale (HADS), used to contemporary determine levels of anxiety and depression experienced by subjects (Herrmann, 1997); the Hamilton Anxiety Rating Scale (HAM-A), used in patients already diagnosed with an anxiety disorder (Maier et al., 1988); the Zung Self-reported Anxiety Scale (Zung SAS), a self-report assessment questionnaire (Zung, 1971); the Depression Anxiety Stress Scale (DASS) (Antony et al., 1998), with answers based on a 4-point Likert scale; the Beck Anxiety Inventory, also based on a 4-point Likert scale (Fydrich et al., 1992); the Modified Dental Anxiety Scale (MDAS) (Humphris et al., 2009); and the Face Anxiety Scale (FAS) (Buchanan and Niven, 2002). Studies were also included when they reported physiological parameters related to the anxious state (such as systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature). Studies were excluded when anxiety outcomes were not among their objectives.

No restrictions were posed for inclusion in terms of study design, even though retrieved studies were separately grouped as Randomized Controlled Trials (RCTs) and Non-Randomized Studies (NRSs). Trials with unclear or partial methodology description were all the same considered eligible to minimize publication bias and maximize retrievable evidence about the topic. These aspects were thoroughly taken into account for their risk-of-bias assessment. Trials were excluded from the qualitative synthesis when essential data were missing. All manuscripts written in English, Italian, French, and Spanish were included.

The following list summarizes the applied PICOS criteria for inclusion and exclusion of studies in the systematic review:

- •

P (Population): patients with anxiety, involved in an anxiety-inducing setting or undergoing an anxiety-inducing activity.

- •

I (Intervention): administration of lavender (all lavender species, any type of formulation, any route of administration).

- •
  C (Comparison): all types of control/comparison.
- •
  O (Outcomes): all possible scales to evaluate anxiety levels and all physiological parameters which indirectly estimate anxiety levels.
- •
  S (Study design): all types of clinical study design.

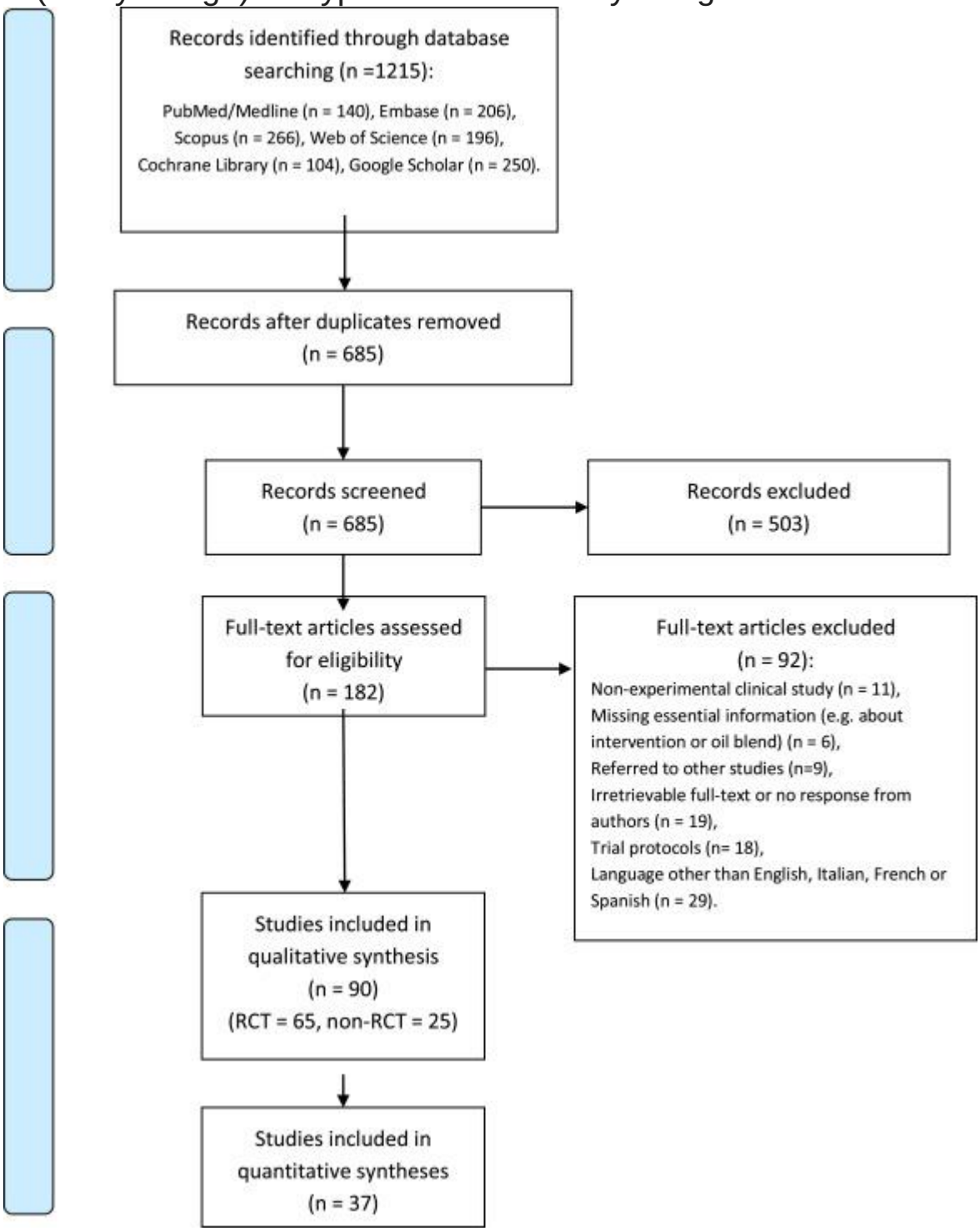

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   Fig. 1. PRISMA flow diagram of the systematic review and meta-analysis (adapted from Liberati et al., 2009).
   Furthermore, the following PICOS criteria for inclusion and exclusion of trials in the meta-analysis were adopted:

- •
  P (Population): patients with anxiety, involved in an anxiety-inducing setting or undergoing an anxiety-inducing activity.
- •
  I (Intervention): oral administration of a standardized lavender product (Silexan®), inhalation or massage with lavender essential oil.
- •
  C (Comparison): usual care, no intervention, sham intervention or placebo, massage without lavender essential oil.
- •
  O (Outcomes): anxiety measured with validated scales only. Systolic Blood Pressure (SBP) was also considered as a physiological measure which indirectly estimates anxiety levels.
- •
  S (Study design): only Randomized Clinical Trials (RCTs). NRSs were excluded from the meta-analysis due to their highly heterogeneous and often poorly described (or even unspecified) methodology.

Data collection process

Once study screening and selection process was completed, data were manually extracted by two investigators independently (C.B., D.D.) from included articles and then summarized in tables (Table 1, Supplementary Tables A, C, D and E). In case of discrepancies, items were independently extracted by a third author (M.A.), and then discussed until consensus was reached. When data were only graphically displayed, they were extracted from graphs with a dedicated plot digitizer (WebPlotDigitizer 4.3). When essential data were missing, authors of the involved study were contacted by email or through ResearchGate®, although no

additional information was retrieved in this way since no response was received. One includible trial was unpublished in its full form and presented as a poster by Kasper and Dienel in 2015 at the Annual Congress of the German Society for Psychiatry and Psychotherapy under the following title: “Effects of Silexan on daily living skills and health-related quality of life in patients with generalized anxiety disorder: results from a randomized, double-blind, placebo controlled trial”. A methodological description and essential data of this study were indirectly retrieved from a review article to which the same researchers contributed as authors (Kasper et al., 2017). In such review article, the study was labeled as “trial A”.

Table 1. Characteristics of RCTs (Randomized Controlled Trials) included in the systematic review.

Author (Year)	**(No. of randomized patients) Population characteristics**[a]	**Age**[b]	**Lavender species**	**Intervention type**[c]	**Interv Grou**
Ayik and Özden (2018)	(96) Patients undergoing colorectal surgery	Adults/Elderly	*Lavandula hybrida*	5% lavender oil diluted in almond oil. Massage performed twice before surgery for 10 min	40
Azima et al. (2015a)	(102) Patients (students) with primary dysmenorrhea	Adults	Not specified	10% lavender oil diluted in olive oil. Massage performed in two areas each for 15 min	34
Azima et al. (2015b)	(102) University non-medical students with primary dysmenorrhea	Adults	Not specified	10% lavender oil diluted in olive oil. Massage performed in two areas each for 15 min	34
Bagheri-Nesami et al. (2017)	(72) Haemodialysis patients	Adults/Elderly	*Lavandula angustifolia*	5% lavender oil diluted in sweet almond oil. Inhalation (in dialysis days for 4 weeks) for 10 min	35
Bahrami et al. (2017)	(90) Patients with Acute Coronary Syndrome	Elderly	Not specified	Lavender oil diluted in almond oil. Massage for some minutes.	45

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
Baksha et al. (2014)	(100) Patients undergoing curettage	Nor reported	*Lavandula angustifolia*	Lavender essential oil frictioned under the nose and inhaled for 60 s	50
Bekhradi and Vakilian (2016)	(112) Female university students with test anxiety	Adults	*Lavandula angustifolia* Mill	10% lavender oil. Inhalation overnight, once a week.	61
Bikmoradi et al. (2015)	(70) Patients after artery bypass surgery	Adults/Elderly	Not specified	2% lavender oil diluted in alcohol. Inhalation: for 20 min on the 2nd and 3rd day after surgery	30
Braden et al. (2009)	(150) Surgical patients	Adults/Elderly	Lavandin (*Lavandula hybrida*)	Lavender oil (1 drop of undiluted oil), inhalation and application to foot	51
Bradley et al. (2009)	(97) Healthy non-smoking participants	Adults	*Lavandula angustifolia*	Lavender capsules (200ul of lavender oil diluted in sunflower oil). Oral administration.	33
Burnett et al. (2004)	(73) Undergraduate students, healthy, non-smokers	Adults	Not specified	Lavender essential oil (5 drops per 30 ml distilled water). Inhalation of 3 drops for 10 min	33
Cruz et al. (2012)	(104) Healthy university students	Adults	*Lavandula angustifolia* Mill	Pure lavender oil, 2 drops on a cotton bud. Inhalation for 2 min	39
Diego et al. (1998)	(40) Medical school staff members	Adults	Not specified	Lavender essential oil 10% in grapeseed oil, 3 drops on a cotton	20

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
				swab placed under the nose for 3 min.	
Dunn et al. (1995)	(93) Intensive-care unit patients	Adults/Elderly	*Lavandula vera*	Aromatherapy massage for 15 min: lavender essential oil diluted to 1% concentration.	21
Effati-Daryani et al. (2015)	(141) Pregnant women at 25th to 28th week gestation	Adults	*Lavandula angustifolia*	Lavender cream (1.25% lavender essential oil diluted in a base cream) administered before bed time on legs for 8 weeks, followed by a footbath (in lavender + footbath group)	Laven 46; La only:
Farshbaf-khalili et al. (2018)	(156) Post-menopausal women	Adults	Not specified	Lavender dried flowers, powder capsules (500 mg per capsule). Oral administration, twice a day for 8 weeks	52
Franco et al. (2016)	(93) Women undergoing breast surgery	Adults	*Lavandula angustifolia*	Lavender oil, 2 drops (2% concentration). Inhalation: 10 min	43
Gnatta et al. (2011)	(35) First year nursing university students	Adults	*Lavandula officinalis*	Lavender oil diluted in a gel base (0.5% lavender oil). Massage 3 times a day for 60 days	13
Graham et al. (2003)	(313) Patients undergoing radiotherapy	Adults/Elderly	Not specified	Lavender, bergamot, cedarwood essential oils blend (2:1:1). Inhalation of 3 drops, for 15–20 min	Not re
Grunebaum et al. (2011)	(30) Patients undergoing Botox	Children/Adolescents	Not specified	Lavender oil diluted in water (3 drops in	Not re

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
	injections for the first time			60 ml water). Inhalation	
Hashemi and Faghih (2018)	(70) University nursing students	Adults	Stoechas variety	lavender oil blend (3 drops of damask rose essence, 10%, 7 drops of lavender essence, 10%). Inhalation for 15 min before the exam onset	35
Hosseini et al. (2016)	(90) Subjects undergoing open heart surgery	Adults	Not specified	Lavender essential oil (2 drops), inhalation for 20 min	45
Howard and Hughes (2008)	(96) Young healthy undergraduates	Adults	Not specified	Lavender essential oil, inhalation	32
Hoya et al. (2008)	(50) Patients undergoing gastroscopy	Adults/Elderly	Not specified	Lavender oil aromatherapy 15 min prior to gastroscopy	26
Hozumi et al. (2017)	(364) Patients undergoing colonoscopy	Adults	Not specified	Lavender oil (0.05 ml of lavender oil diluted in 70 ml tap water) aromatherapy before colonoscopy.	71
Igarashi and Fujita (2010)	(20) Pregnant women	Adults	*Lavandula angustifolia*	Lavender oil (one of the 3 possible oils to choose). Inhalation from aroma pendants	9
Igarashi (2013)	(13) Pregnant women in week 28 of a single pregnancy with a normal course	Adults	*Lavandula angustifolia*	Lavender diffusion, 5 drops of essential oil on an aroma diffuser. 5 min exposition	7
Karadag et al. (2017)	(60) ICU coronary patients	Adults	Not specified	Lavender oil (2%, 2 drops diluted in water) Inhalation	30

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
				every night for 15 days	
Karaman et al. (2016)	(106) Peripheral Venous Cannulation in patients undergoing surgery	Adults	*Lavandula angustifolia*	Lavender oil (2%), 2 drops. Inhalation for 5 min before cannulation	51
Kasper et al. (2010)	(216) "subsyndromal" anxiety disorder syndrome patients	Adults	Silexan (*Lavandula angustifolia*)	Silexan (80 mg) capsules, oral administration. 1 capsule per day, swallowed unchewed	87
Kasper et al. (2014)	(539) Generalized anxiety disorder patients	Adults	Silexan (*Lavandula angustifolia*)	Silexan (160 mg), or Silexan (80 mg) capsules, oral administration. One capsule per die, swallowed unchewed	Silexa 103; S 119
Kasper et al. (2015)	(170) Anxiety-related restlessness and disturbed sleep patients	Adults	Silexan (*Lavandula angustifolia*)	Silexan (80 mg) capsules. Oral administration: 1 capsule per day, swallowed unchewed for 70 days	86
Kasper et al. (2016)	(318) Mixed anxiety depressive disorder patients	Adults	Silexan (*Lavandula angustifolia*)	Silexan (80 mg capsules). Oral administration: 1 capsule per day, swallowed unchewed for 70 days	159
Kasper et al. (2017) ("trial A" by Kasper et al., 2015)	(461) Generalized anxiety disorder patients	Adults	Silexan (*Lavandula angustifolia*)	Silexan at once-daily doses of 10, 40, and 80 mg for 10 weeks	Silexa Silexa SIlexa
Kavurmaci et al. (2015)	(154) Nursing students	Adults	Not specified	Lavender oil (3 drops on cloth). Inhalation for 15 min before, and	42

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
				during the examination.	
Kiani et al. (2016)	(70) Haemodialysis patients	Adults	Not specified	Lavender oil (5%), 2 drops, diluted in sweet almond oil. Inhalation, for 15/20 min, 2 times a day for 4 weeks	35
Kianpour et al. (2016)	(171) Post-partum period women	Not reported	Not specified	Lavender oil, 3 drops. Inhalation 3 times a day, for 4 weeks after discharge from hospital	70
Kritsidima and Newton (2010)	(340) Dental clinic patients	Adults	Not specified	Lavender oil (5 drops diluted in 10cc water) in a candle warmer. Aroma diffusion in the waiting room.	170
Kutlu et al. (2008)	(95) University students	Adults	Not specified	Lavender incenses (10 per classroom). Aroma diffusion 15 min before starting and during examination	50
Lamadah and Nomani (2016)	(60) Patients during labour	Adults	Not specified	Lavender oil (2 drops diluted in 50cc almond oil). Back massage for 20 min during labour	30
Lee et al. (2017)	(132) ICU patients undergoing mechanical ventilation	Not reported	Not specified	Lavender oil (2%). Aromatherapy massage for 20 min, then resting for 20 min	52
Matsumoto and Asakural (2013)	(70) Premenstrual phase college students	Adults	*Lavandula angustifolia*	Lavender oil (10 ul) on a cotton pad for diffusion. Aromatherapy for 45 min	Not re

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
Matsumoto et al. (2017)	(19) Women with premenstrual symptoms, college students	Adults	*Lavandula angustifolia*	Lavender oil (10ul) on a cotton pad for diffusion. Aromatherapy	8
Mirbastegan et al. (2016)	(60) ICU myocardial infarction patients	Adults	Not specified	Lavender oil (drops) on an handkerchief attached to patients' clothes. Inhalation for 30 min 3 times a day, for 3 days	30
Muzzarelli et al. (2006)	(118) Patients undergoing colonoscopy or EGDS	Adults/Elderly	Not specified	Lavender essential oil 3 drops on a cotton ball, inhaled for 5 min at 4in of distance from the nose	61
Najafi et al. (2014)	(70) Myocardial infarction patients	Adults/Elderly	*Lavandula stoechas*	Lavender oil (3 drops). Inhalation (20 min) twice a day for the second and third day of hospitalization	33
Nardarajah et al. (2018)	(100) Patients undergoing third molar extraction	Adults	Not specified	Lavender-sandalwood 100% pure essential oil tabs, attached to patients' abdomen. Aromatherapy: before and during surgery.	50
Nematollahi et al. (2017)	(60) Hospitalized Acute Coronary Syndrome patients	Adults/Elderly	*Lavandula angustifolia*	Lavender-matricaria recutita-neroli essential oil blend (ratio 6:2:0.5). Inhalation for 3 consecutive nights	30
Ozkaraman et al. (2018)	(70) Patients treated with chemotherapy in outpatient units	Adults/Elderly	*Lavandula hybrida*	Lavender oil (3 drops on a piece of cotton). Inhalation during chemotherapy sessions for 1 month	30

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Group
Rajai et al. (2016)	(60) Patients undergoing coronary artery bypass graft surgery	Adults	Not specified	Lavender oil (100%, 2 drops) on a cotton pad into a small container. Inhalation before surgery for 20 min	30
Sanei and Chasmi (2018)	(45) First year high school students	Children/Adolescents	*Lavandula angustifolia*	Fresh extract of lavender, to drink (10 ml of extract mixed in a glass of water). Each night for the period preceding exams (20 days for 2nd group, 3 days for 3rd group)	Group 15.
Seifi et al. (2014)	(70) Patients undergoing CABG	Adults/Elderly	Not specified	Lavender oil (2%, 2 drops in a patch inside an oxygen mask). Inhalation: for 20 mins on the 2nd and 3rd day after surgery	30
Şentürk and Tekinsoy Kartın (2018)	(34) Patients on hemodialysis treatment	Adults/elderly	*Lavandula angustifolia*	Lavender essential oil, 2 drops on a cotton pad inhaled for 30 min before going to bed for 1 week	17
Seyyed-rasooli et al. (2016)	(90) Female patients with burns<20% body surface.	Adults	Not specified	Lavender oil blend (3 drops lavender oil, 15 ml almond oil), aromatherapy massage; Inhalation Aromatherapy: lavender oil blend (7 drops lavender oil, 3 drops Rosa damascene oil)	Laven group massa
Sgoutas-Emch et al. (2001)	(80) Undergraduate university students in stressful situation	Adults	Not specified	Lavender oil, diffusion aromatherapy.Group 1: patients being told they would receive aromatherapy and received the therapy	Group 18

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
				while doing the task; Group 3: patients being not told anything about aromatherapy but received the treatment	
Shahnazi et al. (2012)	(106) Patients undergoing IUD insertion	Adults	Not specified	Lavender oil (10 drops in a bottle with diluted milk), 3 drops of solution on a cotton pad, to inhale for 30 min before and during IUD insertion	53
Soden et al. (2004)	(42) Hospice setting cancer patients	Adults/Elderly	Not specified	Lavender oil + inert carrier oil (sweet almond oil) to a dilution of 1%. Massage: 30 min back massage weekly for 4 weeks	16
Trambert et al. (2017)	(87) Women undergoing image-guided breast biopsy	Adults	Not specified	Lavender-sandalwood aromatherapy tabs (2 ml oils blend), placed on patient's gown during biopsy.	30
Tugut et al. (2017)	(156) Women undergoing gynecological examination	Adults	Not specified	10% lavender essential oil on a lamp diffuser, 15 cm from the table during gynecological examination (15 min)	78
Uzunçakmak and Ayaz Alkaya (2018)	(90) PMS university students	Not reported	*Lavandula angustifolia*	Lavender oil (3,15 ml). Steam inhalation: 3 drops of oil were added to 200 ml hot water, to start at least 10 days (once a day) before the start of menstruation and to	40

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Interv Grou
				end it when the cycle started	
Venkataramana et al. (2016)	(100) Dental clinic patients	Adults	*Lavandula angustifolia, Lavandula stoechas*	Lavender oil, on a candle warmer: aroma diffusion, exposition for 15 min while awaiting in the waiting room	50
Woelk and Schläfke (2010)	(77) GAD (generalized anxiety disorder) patients	Adults	*Lavandula angustifolia* (Silexan)	Silexan capsules (80 mg), oral administration, for 6 weeks	36
Xu et al. (2008)	(48) Physically and psychologically healthy women	Adults	*Lavandula angustifolia*	Robotic Shirodhara treatment (lavender group: 0.3% of lavender-infused sesame oil)	16
Zabirunnisa et al. (2014)	(597) Patients awaiting dental procedures in dental office	Adults	*Lavandula angustifolia*	Lavender oil diluted in water (ratio 1:1) in candle warmers placed in the waiting room. Aroma diffusion: 15 min exposition while in the waiting room	287
Ziyaeifard et al. (2017)	(80) Patients undergoing coronary angiography	Adults	*Lavandula angustifolia*	Lavender oil (5 drops on a piece of cotton wool). Inhalation for 5 min	40

Abbreviations: NR = Not Reported; *Y* = Yes; *N* = No; *H* = High; *U* = Unclear; *L* = Low; STAI = State Trait Anxiety Inventory; HR = Heart Rate; RR = Respiratory Rate; HRV = Heart Rate Variability; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MAP = Mean Arterial Pressure; HAMA = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; SAS = Zung Self-Rating Anxiety Scale; PMS = Premenstrual Syndrome; HADS = Hospital Anxiety and Depression Scale; SIMA = Single Item Math Anxiety scale; APQ = Anxiety Personality Questionnaire; TAI = Test Anxiety Inventory; DASS = Depression Anxiety Stress Scales; VAS = Visual Analogue Scale; POMS = Profile Of Mood States; MDAS = Modified Dental Anxiety Scale; CAS = Clinical Anxiety Scale; BAI = Beck Anxiety Inventory; GSR = Galvanic Skin Response; SPHERE = Somatic and Psychological Health Report.

a
(*N* of randomized patients) Characteristics of studied population. NR = not reported.
b
Children/Adolescents (<18 years old); Adults (18–65 years old); Elderly (>65 years old).

c
Intervention type (lavender preparation and way of administration, dosage, brief description of the intervention).

d
Intervention group (number of actually analyzed patients).

e
Control group 1 (type of control, number of actually analyzed patients).

f
Control group 2, if present (type of control, number of actually analyzed patients).

g
Anxiety outcome/s (study objectives are omitted because it is implied that trails aim to test lavender intervention efficacy).

h
Significant change-from-baseline (pre-post) results regarding at least one anxiety outcome measure *within intervention* group: Y if $p < 0.05$; N if $p \geq 0.05$. NR: not reported.
i
Significant change-from-baseline (pre-post) results regarding at least one anxiety outcome measure *within control* group: Y if $p < 0.05$; N if $p \geq 0.05$; NR: not reported.
j
Significant difference of anxiety levels *between* groups *after* intervention: Y if $p < 0.05$; N if $p \geq 0.05$. NR: not reported.
k
Authors' conclusions: Y (intervention is effective); N (intervention is not effective); U (it is unclear whether intervention is effective or not).

l
Overall risk of bias using Cochrane tool with Performance bias as a non-key domain.

Data items

Collected data from included articles were the following ones: first author's name and year of publication, study design (and if a “waiting list” approach was adopted for the control group), objectives, type of anxiety, age and characteristics of studied population (including relevant patients’ comorbidities and anxiety levels at baseline), number of participants, number of patients evaluated for eligibility and number of randomized patients in RCTs, lavender species, characteristics of intervention (lavender preparation and route of administration, dosage, brief description of the intervention), number of actually analyzed patients in the intervention group, characteristics of control/s (type of control/comparison, number of actually analyzed patients),

sampling time, summary of results, reported adverse events of lavender administration (and quantity if present), whether change-from-baseline of at least one anxiety outcome measure within intervention group was significant ($p < 0.05$), whether change-from-baseline of at least one anxiety outcome measure within control group was significant ($p < 0.05$), if end-of-study differences between intervention and control group were significant ($p < 0.05$), outcome measurement values in intervention and control groups, the authors' conclusions.

Risk of bias in individual studies

The risk of bias for each included RCT was independently assessed by two investigators (D.D., C.B.) following the criteria of the Cochrane risk-of-bias tool for trials. Disagreements were discussed with a third investigator (M.A.) until consensus was reached.

In order to better estimate the quality of each included RCT, overall risk of bias was assessed in two ways, both considering performance bias a key domain, and considering it a non-key domain, thus excluding it from the overall evaluation (Supplementary Table B). In the second type of assessment, performance bias was not considered a key domain because in studies involving the inhalation or topical application of lavender essential oil, these specific ways of administration (other than the oral one) make lavender smell hard to blind and easy to be recognized among other scents. Detection bias was considered low when questionnaires were delivered by a blind researcher and unclear when self-completed by patients or when the method of administration was not indicated. Studies were considered at high risk of bias when there was a high risk of bias in at least one key domain or unclear risk of bias in at least two key domains. Studies were considered at unclear risk of bias if only one key domain had an unclear risk of bias. If all key domains had a low risk of bias, the risk of bias of the entire study was reported to be low too.
The risk-of-bias assessment was only performed for RCTs, since they were the majority of included studies and they provided the highest level of evidence. Additionally, NRSs were in general poorly described, they didn't often provide sufficient information about study participants, conduction, drop-out rates, as well as results, or

they appeared excessively inaccurate in terms of experimental methodology.

Furthermore, all trials using the “waiting list” approach design were reported in the “Results” section of the article in order to account for potential additional biases leading to an artificial inflation of intervention effect estimates (Cunningham et al., 2013).

Summary measures

In each meta-analysis including only trials in which anxiety levels were measured with the same validated scale, mean difference was used as a measure of effect size. In the last two meta-analyses, standardized mean difference (Hedges’ g) was adopted as a measure of effect size since it was decided to pool data from studies assessing the same outcome (anxiety) measured with different validated anxiety scales. When sample standard deviations were not available, they were estimated from reported confidence intervals or standard errors with proper statistical tools (Higgins and Green, 2011; Weir et al., 2018). When only sample medians, as well as minimum and maximum values, were available, sample means and standard deviations were calculated with validated formulas accepting the assumption that the original data distribution was normal in order to maximize retrievable data and minimize publication bias (Wan et al., 2014). Considering high heterogeneity of included studies, a random-effect model was adopted to better estimate overall size effects.

Synthesis of results

Results were summarized in tables and discussed to obtain a qualitative synthesis, both from included RCTs (Table 1) and from NRSs (Supplementary Table A). Retrieved data were critically appraised and reported according to the characteristics of study design, population, intervention, control, outcomes, efficacy of lavender for anxiety management, adverse effects, and controversial information. Detailed characteristics of samples involved in all included studies, as well as baseline and end-of-study anxiety levels of included RCTs were reported in the supplementary materials (Supplementary Tables D and E). Results of included NRSs were only briefly mentioned in the present

manuscript, and were fully described in the supplementary materials (Supplementary Table A).
A quantitative synthesis was then performed. The software used to perform the meta-analysis was “Review Manager” (RevMan, version 5.3). An analysis was also conducted in “R” (R Development Core Team, 2014) using RStudio ver. 1.2.1335 and the packages “meta” (Schwarzer et al., 2015) and “metafor” (Viechtbauer, 2010). Included studies were heterogeneous in terms of design, population, intervention, comparison, so it was necessary to apply the strictest criteria when selecting trials for inclusion in the meta-analysis, in order to achieve the best possible homogeneity without impeding from performing a quantitative assessment. Subgroup analyses were then used to investigate possible differences between groups of trials sharing similar characteristics. Pre-post effect size meta-analysis (namely the use of post-test data as intervention values and pre-test data as control values) was excluded due to possibly biased outcomes (Cuijpers et al., 2017). To achieve homogeneity among extracted data, only comparable items of the various anxiety-related parameters (intended as scales, questionnaires, physiological values) were considered. On the basis of available data it was decided to perform seven meta-analyses. The first meta-analysis (Fig. 2) summarized the effects of Silexan® at a dose of 80 mg/die on anxiety levels (pre-post intervention changes in HAMA total score) compared to placebo.

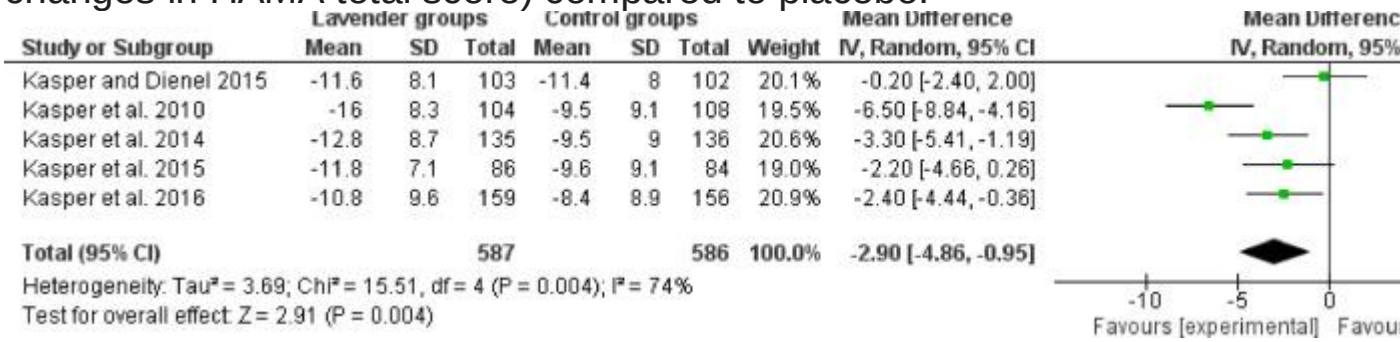

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Fig. 2. Forest plot referred to the meta-analysis about effects of Silexan® at a dose of 80 mg/die on anxiety levels (pre-post intervention changes in HAMA total score) compared to placebo. Description: Anxiety levels (measured with HAM-A questionnaire) mean changes-from-baseline after intervention (Silexan® 80 mg/die) compared to anxiety levels mean changes-from-baseline after placebo. Means and standard deviations are reported in

columns and a random-effect model was adopted to better estimate overall size effects.

The second meta-analysis (Fig. 3) summarized the effects of oral administration of Silexan® at a dose of 80 mg/die on anxiety levels (pre-post intervention changes in Zung SAS score) compared to placebo.

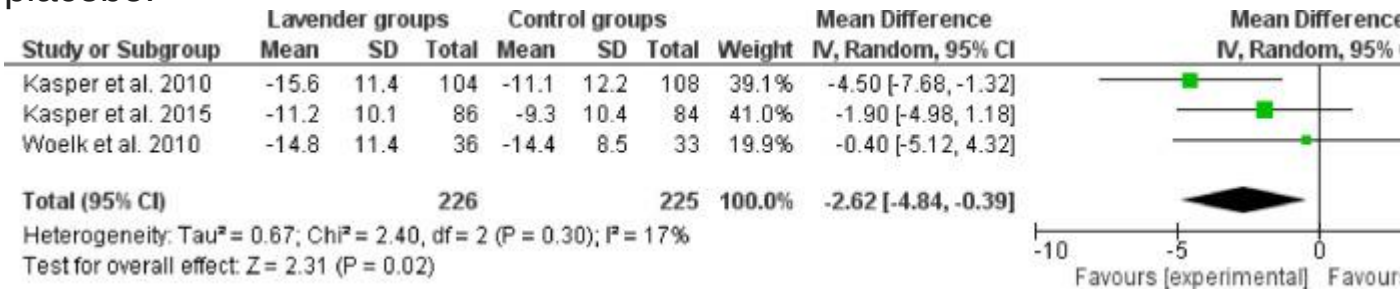

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Fig. 3. Forest plot referred to the meta-analysis about the effects of oral administration of Silexan® at a dose of 80 mg/die on anxiety levels (pre-post intervention changes in Zung SAS score) compared to placebo. Description: Anxiety levels (measured with Zung SAS score) mean changes-from-baseline after intervention (Silexan® 80 mg/die) compared to anxiety levels mean changes-from-baseline after placebo. Means and standard deviations are reported in columns and a random-effect model was adopted to better estimate overall size effects.

The third meta-analysis (Fig. 4) summarized the effects of inhalation of lavender essential oil on state anxiety levels (STAI-S score after intervention) compared to no intervention or usual care.

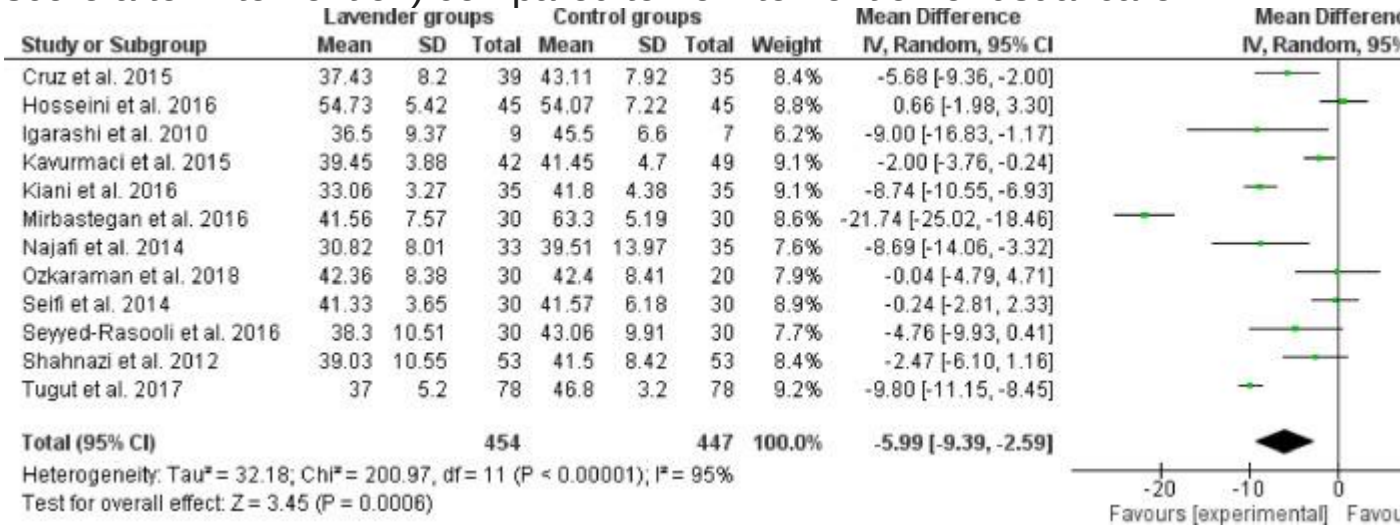

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Fig. 4. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on anxiety levels (STAI-S score after intervention) compared to no intervention or usual care.
Description: Anxiety levels (measured with STAI-S questionnaire) after intervention (lavender essential oil inhalation) compared to anxiety levels after no intervention or usual care. Means and standard deviations are reported in columns and a random-effect model was adopted to better estimate overall size effects.
The fourth meta-analysis (Fig. 5) summarized the effects of inhalation of lavender essential oil on trait anxiety levels (STAI-T score after intervention) compared to no intervention or usual care.

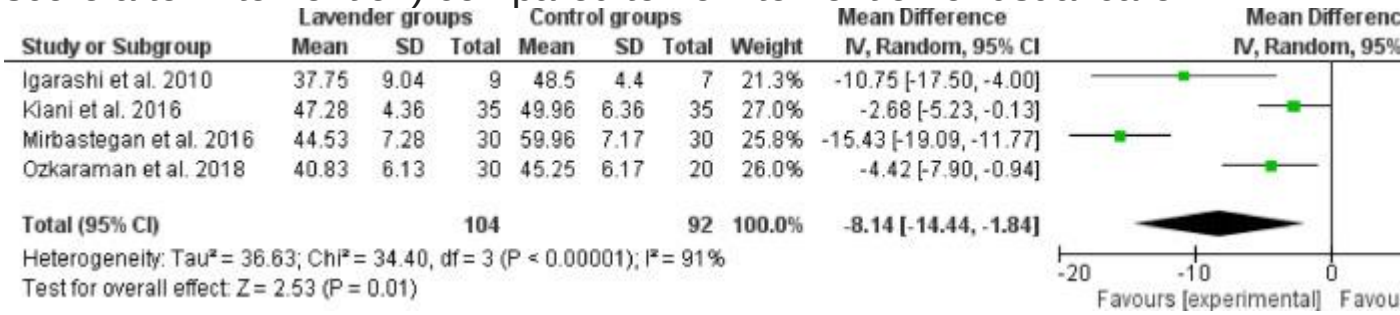

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Fig. 5. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on anxiety levels (STAI-T score after intervention) compared to no intervention or usual care.
Description: Anxiety levels (measured with STAI-T questionnaire) after intervention (lavender essential oil inhalation) compared to anxiety levels after placebo. Means and standard deviations are reported in columns and a random-effect model was adopted to better estimate overall size effects.
The fifth meta-analysis (Fig. 6) displayed the effects of inhalation of lavender essential oil on systolic blood pressure (pre-post intervention variations) compared to no intervention or sham intervention (distilled water or oil without lavender).

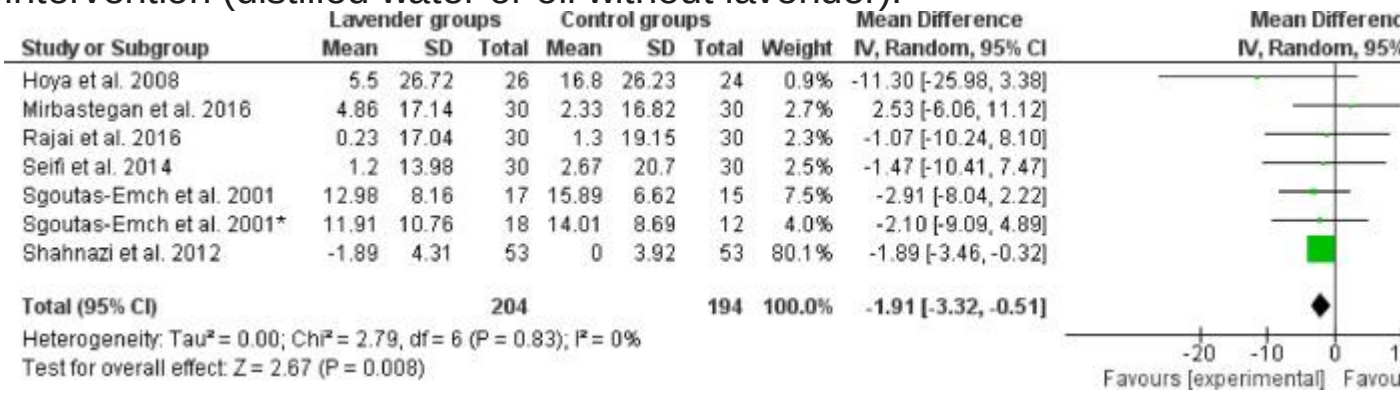

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Fig. 6. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on systolic blood pressure (mean changes-from-baseline) compared to no intervention or sham intervention (distilled water or oil without lavender). Description: systolic blood pressure (measured in mmHg) mean changes-from-baseline after intervention (lavender essential oil inhalation) compared to systolic blood pressure after no intervention or sham intervention (distilled water or oil without lavender). Means and standard deviations are reported in columns and a random-effect model was adopted to better estimate overall size effects.

The sixth meta-analysis (Fig. 7) summarized the overall effects of inhalation of lavender essential oil on anxiety levels (pre-post intervention variations assessed with any validated scale) regardless of comparison type.

	Lavender			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bagheri-Nesami et al. 2017	-0.65	4.07	35	-1.06	4.27	37	4.4%	0.10 [-0.37, 0.56]
Baksha et al. 2014	-13.09	8.66	50	-1.32	12.96	50	4.5%	-1.06 [-1.48, -0.64]
Bekhradi et al. 2016	-7.79	17.14	61	-4.95	13.31	42	4.6%	-0.18 [-0.57, 0.21]
Bikmoradi et al. 2015	-8.1	2.3	30	-7.57	2.87	30	4.3%	-0.20 [-0.71, 0.31]
Diego et al. 1998	-3.11	9.16	20	-7	8.18	20	4.0%	0.44 [-0.19, 1.07]
Hosseini et al. 2016	-2	1.14	45	-1.11	1.46	45	4.5%	-0.67 [-1.10, -0.25]
Hoya et al. 2008	0	0.93	26	0.5	0.86	24	4.1%	-0.55 [-1.11, 0.02]
Igarashi et al. 2010	2	8.22	9	4.25	7.93	7	3.0%	-0.26 [-1.26, 0.73]
Kadarag et al. 2017	-3.07	3.45	30	0.77	2.86	30	4.2%	-1.20 [-1.75, -0.64]
Karaman et al. 2016	-0.88	1.1	51	-0.14	1.02	50	4.6%	-0.69 [-1.09, -0.29]
Kiani et al. 2016	-6.05	5.32	35	-0.68	5.08	35	4.3%	-1.02 [-1.52, -0.52]
Kianpour et al. 2016	-0.92	2.46	70	0.83	3.77	70	4.7%	-0.55 [-0.88, -0.21]
Matsumoto et al. 2017	-2.9	7.09	8	-2.3	5.72	9	3.1%	-0.09 [-1.04, 0.86]
Mirbastegan et al. 2016	-18.7	8.56	30	6.7	8.78	30	3.7%	-2.89 [-3.63, -2.15]
Najafi et al. 2014	-12.33	10.72	33	-1.8	13.46	35	4.3%	-0.85 [-1.35, -0.35]
Ozkaraman et al. 2018	-3.97	6.58	30	-0.15	6.61	20	4.1%	-0.57 [-1.15, 0.01]
Rajai et al. 2016	-0.17	1.75	30	1.9	2.3	30	4.2%	-1.00 [-1.54, -0.46]
Seifi et al. 2014	-7.4	4.54	30	-6.43	6.62	30	4.3%	-0.17 [-0.68, 0.34]
Senturk et al. 2018	-5.82	3.4	17	2.7	5.49	17	3.5%	-1.82 [-2.64, -1.01]
Seyyed-Rasooli et al. 2016	-6.43	10.58	30	0.53	5.11	30	4.2%	-0.83 [-1.36, -0.30]
Sgoutas-Emch et al. 2001	3.18	2.72	17	2.06	3.15	15	3.8%	0.37 [-0.33, 1.07]
Shahnazi et al. 2012	-4.19	6.39	53	-0.74	4.15	53	4.6%	-0.64 [-1.03, -0.25]
Tugut et al. 2017	-2.8	5.22	78	8.7	5.65	78	4.6%	-2.10 [-2.50, -1.71]
Uzuncakmak et al. 2018	-8.7	5.77	40	-1.9	7.45	37	4.4%	-1.02 [-1.49, -0.54]
Total (95% CI)			**858**			**824**	**100.0%**	**-0.73 [-1.00, -0.46]**

Heterogeneity: Tau² = 0.37; Chi² = 152.27, df = 23 (P < 0.00001); I² = 85%
Test for overall effect: Z = 5.34 (P < 0.00001)

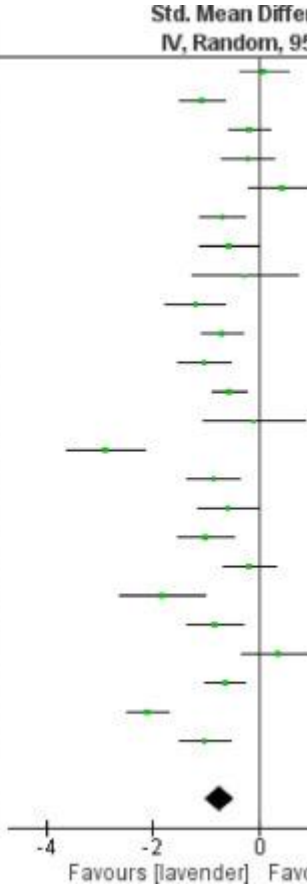

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Fig. 7. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on anxiety levels (pre-post intervention variations assessed with any validated scale)

regardless of comparison type. Description: Anxiety levels (measured with any validated scale) mean changes-from-baseline after intervention (lavender essential oil inhalation) compared to any comparison type. Means and standard deviations are reported in columns and a random-effect model was adopted to better estimate overall size effects.

The seventh meta-analysis (Fig. 8) described the effects of massage with lavender oil on anxiety levels (measured with any validated scale) compared to other physical therapies (reflexology or massage without oil) or usual care.

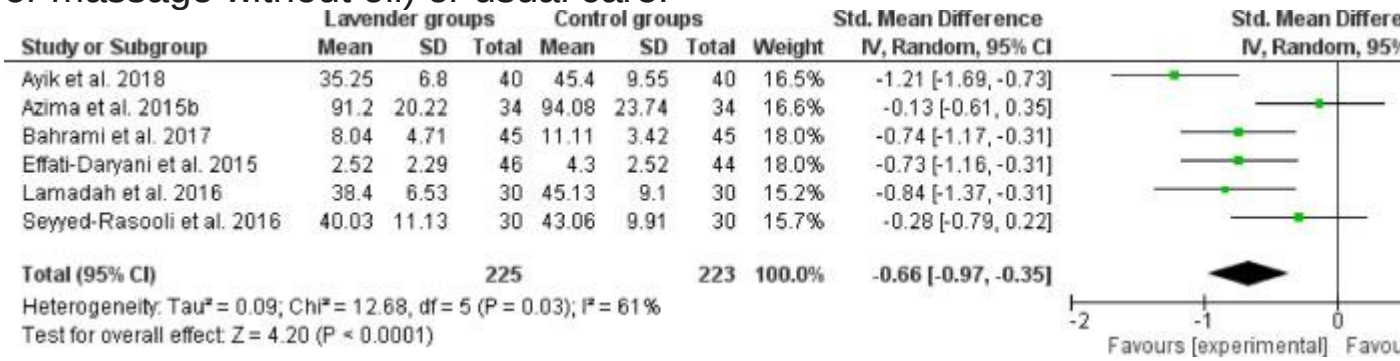

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Fig. 8. Forest plot referred to the meta-analysis about the effects of massage with lavender oil on anxiety levels (measured with any validated scale) compared to other physical therapies (reflexology or massage without oil) or usual care. Description: Anxiety levels (measured with any validated scale) after intervention (massage with lavender essential oil) compared to other physical therapies (reflexology or massage without oil) or usual care. Means and standard deviations are reported in columns and a random-effect model was adopted to better estimate overall size effects.

I^2 was used as a measure of consistency. I^2 values of 25%, 50%, and 75% were interpreted as representing small, moderate and high levels of heterogeneity (Higgins et al., 2003). In particular, I^2 < 25% was considered very low, 25% < I^2 < 50% moderate, 50% < I^2 < 75% high, whereas I^2 > 75% was rated as very high.

Risk of bias across studies

When possible (at least 10 studies included in the analysis), publication bias across studies included in the quantitative synthesis was assessed with funnel plots following the Cochrane

recommendations (Higgins and Green, 2011). In each plot, symmetry and a funnel-shaped arrangement of points representing included studies suggested a low risk of publication bias, whereas asymmetry or an irregular shape indicated a higher risk of publication bias.
In order to estimate the risk of publication bias beyond a simple visual assessment of funnel plots, Egger's tests were performed with “R” for all meta-analyses which included at least ten studies. Each meta-analysis was considered unbiased when the *p* value of the Egger's test was not statistically significant (Egger et al., 1997). The p-curve method (Simonsohn et al., 2014a) was adopted to further assess the risk of bias across studies, and to detect any potential “p-hacking”. R and “compute.es” (Del Re, 2013), “esc” (Lüdecke, 2018), “stringr” and “poibin” packages were used (Hong, 2011; Harrer et al., 2019). The p-curve method was also employed to exclude possible selective reporting bias among included studies with significant results, and to estimate the underlying average statistical power of meta-analyses (in other words, to test if the sets of studies were, on average, powered enough to detect a true effect of studied intervention) (Simonsohn et al., 2014a,b). The estimation of the average statistical power with the p-curve method can help to correct for the inflated estimates that arise from the publication of results intentionally modified to be significant (“p-hacking”). With the p-curve method, no arbitrary post-hoc assumptions are needed to evaluate the statistical power of a set of studies (Simonsohn et al., 2014a,b). Information needed for the p-curve disclosure table (Simonsohn et al., 2014a) are retrievable from Table 1 and from Forest plots.

Additional analyses

When change-from-baseline of anxiety levels had to be calculated, a sensitivity analysis was performed to study whether changing the degree of correlation between pre- and post-intervention anxiety levels could significantly affect the overall results. Results of these analyses were graphically reported.

In any meta-analysis, when one or more outliers were recognized after a visual assessment of corresponding Forest and funnel plots, an outlier detection analysis was performed using “R” (package

“dplyr” Wickham et al., 2019) to identify all those studies which presented an upper confidence interval inferior to the lower confidence interval of the overall mean difference. When one or more outliers were detected, a leave-one-out (or a subgroup) sensitivity analysis was performed, in order to assess to what extent excluding the outlying trial/s could affect the overall effect size and heterogeneity. Results of these analyses were described in the Discussion section.
When studies at high risk of bias were identified in each meta-analysis, a sensitivity subgroup analysis was performed, in order to test whether there were some significant changes in obtained results after the exclusion of trials at high risk of bias. Other subgroup analyses were performed to test possible differences between studies with specific population characteristics.
Afterwards, two meta-regressions were performed. In the first one, studies included in the meta-analysis reported in Fig. 4 (lavender inhalation, STAI-S questionnaire) were analyzed, and STAI-S baseline anxiety levels were selected as a moderator. In the second one, studies included in the meta-analysis reported in Fig. 7 (lavender inhalation, any validated anxiety scale) were analyzed, and the setting type as well as the duration over time of lavender administration were chosen as moderators. A mixed-effect model was used, and a Restricted Maximum Likelihood (REML) method was adopted as an estimator for Tau^2 in both meta-analyses. Potential collinearity among moderators was assessed using the conditional number method, due to the fact that all moderators were nominal categorical ones. Robustness of the model was evaluated with the permutation test. Details of these additional analyses were displayed in the Supplementary Fig. 11.

Results

Study selection

After searching electronic databases, 1215 articles were identified and collected. When duplicates were removed, 685 articles remained for the screening process. 503 articles were excluded after an evaluation based on the assessment of their title and abstract. Then, 182 articles underwent full-text screening and 92 of them were excluded with motivations, as reported in Fig. 1. Finally,

90 articles were included in the qualitative synthesis and 37 articles were included in the quantitative synthesis. Details of study screening and selection process were reported in a dedicated flowchart (Fig. 1). As reported in the methods section, results of included NRSs were fully described in the supplementary materials (Supplementary Table A).

Qualitative synthesis of results

Design of included studies

After full-text assessment, 90 articles were considered eligible for qualitative synthesis (Fig. 1): 65 of them were RCTs (Ayik and Özden, 2018; Azima et al., 2015a,b; Bagheri-Nesami et al., 2017; Bahrami et al., 2017; Bakhsha et al., 2014; Bekhradi and Vakilian, 2016; Bikmoradi et al., 2015; Braden et al., 2009; Bradley et al., 2009; Burnett et al., 2004; Cruz et al., 2012; Dunn et al., 1995; Effati-Daryani et al., 2015; Farshbaf-Khalili et al., 2018; Field et al., 2005; Franco et al., 2016; Gnatta et al., 2011; Graham et al., 2003; Grunebaum et al., 2011; Hashemi and Faghih, 2018; Hosseini et al., 2016; Howard and Hughes, 2008; Hoya et al., 2008; Hozumi et al., 2017; Igarashi, 2013; Igarashi and Fujita, 2010; Karadag et al., 2017; Karaman et al., 2016; Kasper et al., 2017, 2016, 2015, 2014, 2010; Kavurmacı et al., 2015; Kiani et al., 2016; Kianpour et al., 2016; Kritsidima and Newton, 2010; Kutlu et al., 2008; Lamadah and Nomani, 2016; Lee et al., 2017; Matsumoto et al., 2017; Matsumoto and Asakura, 2013; Mirbastegan et al., 2016; Muzzarelli et al., 2006; Najafi et al., 2014; Nardarajah et al., 2018; Nematollahi et al., 2017; Özkaraman et al., 2018; Rajai et al., 2016; Sanei and Chasmi, 2018; Seifi et al., 2014; Şentürk and Tekinsoy Kartın, 2018; Seyyed-Rasooli et al., 2016; Sgoutas-Emch et al., 2001; Shahnazi et al., 2012; Soden et al., 2004; Trambert et al., 2017; Tugut et al., 2017; Uzunçakmak and Ayaz Alkaya, 2018; Venkataramana et al., 2016; Woelk and Schläfke, 2010; Xu et al., 2008; Zabirunnisa et al., 2014; Ziyaeifard et al., 2017), and 25 were NRSs (Cho et al., 2013; Conrad and Adams, 2012; Davidson, 2002; Domingos and Braga, 2015; Dong and Jacob, 2016; Fayazi et al., 2011; Fißler and Quante, 2014; Imanishi et al., 2009; Imura et al.,

2006; Iokawa et al., 2018; Itai et al., 2000; Jaruzel et al., 2019; Kim and Hwangbo, 2010; Kuriyama et al., 2005; Lehrner et al., 2005; Louis and Kowalski, 2002; Ludvigson and Rottman, 1989; McCaffrey et al., 2009; Moorman Li et al., 2017; Rho et al., 2006; Saritaş et al., 2018; Stange et al., 2007; Takeda et al., 2008; Wotman et al., 2017; Yayla and Ozdemir, 2019). Main data of included studies were summarized in Table 1 (RCTs) and in Supplementary Table A (NRSs). Additionally, to improve the readability of this part of the review, references of the most relevant descriptive data (PICOS characteristics) regarding all studies included in the qualitative synthesis were collected in Supplementary Table C.
In one trial only, the design implied a "waiting list" approach in the control group (Sgoutas-Emch et al., 2001).

Population

In general, characteristics of studied population and experimental settings were heterogeneous, as well as the type of anxiety, varying from primary anxiety disorder, to secondary anxiety, induced by specific situations or conditions (such as watching anxiogenic video clips, undergoing invasive procedures or attending an exam). This was valid both for RCTs and for NRSs. Noticeably, for some ways of administration like inhalation, it was possible to identify that the majority of study settings and situations in which participants were involved belonged to two groups: high anxiety-inducing situations and mild anxiety-inducing situations. All characteristics of study samples, along with details regarding comorbidities, were reported in Supplementary Table D.
The median value of study population numerosity was 90 for RCTs (with a minimum of 13 and a maximum of 597 patients).

Study population was mostly composed of adults and/or elderly (>18 years old), except from two (2) RCTs (Grunebaum et al., 2011; Sanei and Chasmi, 2018) that considered the pediatric population.

Intervention

Included RCTs (Table 1) presented various routes of lavender administration: inhalation was the most frequent intervention, and it

was reported in 33 RCTs (Supplementary Table C). In all trials using inhalation-based interventions, lavender was administered in the form of essential oil and as the predominant part of a blend of different essential oils in 4 studies (Graham et al., 2003; Hashemi and Faghih, 2018; Nematollahi et al., 2017; Seyyed-Rasooli et al., 2016). Other ways to administer lavender included aromatherapy with an aroma diffuser, lavender essential oil topically applied by massage therapy, and capsules with lavender essential oil standardized in linalool and linalyl-acetate concentration (Silexan®) (Supplementary Table C). When used for massage therapy, lavender essential oil was usually diluted in almond or sesame oil for massage. In aromatherapy studies, lavender essential oil was usually diluted into water, or, alternatively, a specific diffuser, or incense, or aroma tabs were used.
In 38 RCTs one single dose of lavender was administered, whereas in 27 trials lavender was given to patients on a chronic basis (Supplementary Table C).
Among lavender subspecies, the most frequently used one in included studies was *L. angustifolia (*synonyms*: L. vera or L. officinalis)*, which was administered in 28 RCTs (Supplementary Table C). Other subspecies included *L. hybrida* (also called *L. × intermedia or lavandin*) and *L. stoechas*, as shown in Table 1.

Control

A high level of heterogeneity was found in control conditions (no intervention or usual care, placebo, or other treatments).

Among RCTs in which lavender was administered through inhalation, 13 studies had usual care as control, in one study usual care and tea tree oil were administered as a comparison (Özkaraman et al., 2018), whereas placebo (water or other oils) was given to control groups in 17 studies (Supplementary Table C). Only 5 studies had no intervention in the control group (Supplementary Table C), whereas in one trial both no intervention and peppermint oil were used as controls (Cruz et al., 2012).
Among RCTs in which lavender was administered through aromatherapy, placebo was the most frequent control condition, followed by rest, and no intervention (Supplementary Table C). In

one study, lavender essential oil was used as a control and compared to the administration of Yuzu (*Citrus Junos*) oil to assess its anxiolytic effects (Matsumoto et al., 2017).
Among RCTs in which lavender was orally administered, control conditions were placebo pills, lorazepam, paroxetine, and, in one study, no intervention (Sanei and Chasmi, 2018).
Among RCTs in which lavender oil was applied by massage therapy, control conditions included usual care alone, usual care or placebo (Soden et al., 2004), no intervention or muscular exercise (Azima et al., 2015b), placebo or music therapy (Lee et al., 2017), placebo only (Lamadah and Nomani, 2016), as well as placebo or rest (Dunn et al., 1995).

Outcomes

The most frequently used scale to measure anxiety levels was the Spielberger's State and Trait Anxiety Inventory (STAI), employed in 33 RCTs (Supplementary Table C). Types of outcome measures of included RCTs were reported in the Supplementary Table E.
Other scales used to assess anxiety were: the Hamilton Anxiety Rating Scale (HAMA), the Hamilton Depression Rating Scale (HAMD), the Zung Self-Rating Anxiety Scale (SAS), the Hospital Anxiety and Depression Scale (HADS), the Single Item Math Anxiety scale (SIMA), the Anxiety Personality Questionnaire (APQ), the Test Anxiety Inventory (TAI), the Depression Anxiety Stress Scales (DASS), the Visual Analogue Scale (VAS), the Profile Of Mood States (POMS), the Modified Dental Anxiety Scale (MDAS), the Clinical Anxiety Scale (CAS), the Beck Anxiety Inventory (BAI), the Somatic, Psychological Health Report (SPHERE), and the Face Anxiety Scale (FAS).
In some studies, physiological parameters were also measured to evaluate the effects of lavender on the autonomic nervous system response and the most frequently used parameter was SBP, assessed in 13 RCTs (Supplementary Table C). Other physiological parameters included diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR), as shown in Table 1.

Efficacy

When considering the results of included studies, 54 RCTs showed at least a significant ($p < 0.05$) pre-post improvement in anxiety levels within lavender intervention groups or a significant post-test difference between groups favoring lavender groups (Supplementary Table C). Baseline and end-of-study anxiety levels were reported in the Supplementary Table E. At baseline, anxiety levels of participants analyzed in all included RCTs ranged from moderate to severe (Supplementary Table E).
44 RCTs reported a significant post-test improvement in anxiety levels between intervention and control groups (see Supplementary Table C). Among the subgroup of RCTs which did not report significant post-test difference in anxiety levels between intervention and control groups, 10 studies (Azima et al., 2015a,b; Bakhsha et al., 2014; Braden et al., 2009; Diego et al., 1998; Dunn et al., 1995; Igarashi, 2013; Matsumoto et al., 2017; Sgoutas-Emch et al., 2001; Xu et al., 2008) displayed at least a significant pre-post improvement in anxiety levels within the sole intervention lavender group, while no significant amelioration was reported for controls. This subgroup may still be taken into consideration to evaluate the efficacy of lavender interventions, although it represents a weaker level of evidence regarding the efficacy of studied intervention.
In 51 RCTs, authors reported a favorable conclusion, in 11 trials they did not consider the intervention useful, and in 3 studies they did not report a clear conclusion about the efficacy of intervention (Supplementary Table C).

Adverse effects

Only a limited number of included studies reported adverse effects potentially ascribable to lavender administration. The main adverse effects were reported in 7 studies, 6 RCTs (Farshbaf-Khalili et al., 2018; Kasper et al., 2016, 2015, 2014, 2010; Woelk and Schläfke, 2010) and one NRSs (Stange et al., 2007), and were headaches, palpitations, infections, and gastrointestinal disorders (eructation, diarrhea, breath odor, and dyspepsia). None of reported adverse effects were serious ones.

Controversial data

Results data reported from Venkataramana et al. (2016) are identical to those reported from Zabirunnisa et al. (2014), although the authors of the two studies are completely different. This controversial finding was reported to the editors of involved scientific journals. A response was received from the editor-in-chief of the journal in which the article by Zabirunnisa et al. (2014) was published, assuring that the COPE guidelines would be followed for an adequate dispute resolution.

Risk of bias within studies

Results of the risk-of-bias assessment were summarized in Table 1. For further details, refer to Supplementary Table B.
When considering performance bias as a key domain, the overall risk of bias was rated as low in 3 RCTs (Bikmoradi et al., 2015; Kasper et al., 2010; Shahnazi et al., 2012), unclear in 4 RCTs (Farshbaf-Khalili et al., 2018; Hashemi and Faghih, 2018; Hozumi et al., 2017; Kasper et al., 2014), and high in the other 58 RCTs (Supplementary Table C).
When performance bias was considered a non-key domain, the overall risk of bias was rated as low in 9 RCTs (Bikmoradi et al., 2015; Braden et al., 2009; Hashemi and Faghih, 2018; Hozumi et al., 2017; Karaman et al., 2016; Kasper et al., 2010; Lee et al., 2017; Özkaraman et al., 2018; Shahnazi et al., 2012), unclear in 10 RCTs (Bahrami et al., 2017; Effati-Daryani et al., 2015; Farshbaf-Khalili et al., 2018; Franco et al., 2016; Hosseini et al., 2016; Kasper et al., 2014; Kavurmacı et al., 2015; Najafi et al., 2014; Seyyed-Rasooli et al., 2016; Ziyaeifard et al., 2017), and high in the other 46 RCTs (Supplementary Table C).

Quantitative synthesis of results

After article selection, 37 RCTs were included in the quantitative synthesis (Ayik and Özden, 2018; Azima et al., 2015a; Bagheri-Nesami et al., 2017; Bahrami et al., 2017; Bakhsha et al., 2014; Bekhradi and Vakilian, 2016; Bikmoradi et al., 2015; Cruz et al., 2012; Diego et al., 1998; Effati-Daryani et al., 2015; Hosseini et al., 2016; Hoya et al., 2008; Igarashi and Fujita, 2010; Karadag et al., 2017; Karaman et al., 2016; Kasper et al., 2017, 2016, 2015, 2014, 2010; Kavurmacı

et al., 2015; Kiani et al., 2016; Kianpour et al., 2016; Lamadah and Nomani, 2016; Matsumoto et al., 2017; Mirbastegan et al., 2016; Najafi et al., 2014; Özkaraman et al., 2018; Rajai et al., 2016; Seifi et al., 2014; Şentürk and Tekinsoy Kartın, 2018; Seyyed-Rasooli et al., 2016; Sgoutas-Emch et al., 2001; Shahnazi et al., 2012; Tugut et al., 2017; Uzunçakmak and Ayaz Alkaya, 2018; Woelk and Schläfke, 2010) and seven meta-analyses were performed.

Five trials (Kasper et al., 2017, 2016, 2015, 2014, 2010) were included in the first meta-analysis, evaluating the effects of oral administration of Silexan®, at a dose of 80 mg/die, on levels of anxiety measured with the Hamilton's Anxiety Rating Scale (HAMA), compared to placebo (Fig. 2). Since standard deviations of the pre-post mean difference of anxiety levels in each group were not reported in Kasper et al. (2015), it was decided to impute the missing change-from-baseline standard deviation with a formula using the correlation coefficient (Higgins and Green, 2011). In place of a sensitivity analysis, since the four included studies were conducted by the same group, thus being very homogeneous in their design and characteristics, the correlation coefficient was estimated from another included study reported in considerable detail (Kasper et al., 2010) where all the variables needed to calculate it were available ($r = 0.416$). Therefore, the overall mean difference was MD = −2.90 [95% CI −4.86 to −0.95]; $p = 0.004$; $I^2 = 74\%$.

Three trials (Kasper et al., 2015, 2010; Woelk and Schläfke, 2010) were included in the second meta-analysis, whose purpose was to assess the effects of oral administration of Silexan®, at a dose of 80 mg/die on levels of anxiety measured with the Zung Self Rating Anxiety Scale (Zung SAS), compared to placebo (Fig. 3). The result of this analysis indicated a significant tendency in favor of lavender with an overall effect size of MD = −2.62 [95% CI −4.84 to −0.39]; $p = 0.02$; $I^2 = 17\%$.

Twelve trials (Cruz et al., 2012; Hosseini et al., 2016; Igarashi and Fujita, 2010; Kavurmacı et al., 2015; Kiani et al., 2016; Mirbastegan et al., 2016; Najafi et al., 2014; Özkaraman et al., 2018; Seifi et al., 2014; Seyyed-Rasooli et al., 2016; Shahnazi et al., 2012; Tugut et al., 2017) were included in the third meta-analysis, whose purpose was to evaluate the effects of lavender essential oil inhalation on levels of state

anxiety measured with the Spielberger's State Anxiety Inventory (STAI-S), compared to no intervention or usual care (Fig. 4). The result of this analysis significantly favored lavender-based interventions with an overall effect size of MD = −5.99 [95% CI −9.39 to −2.59]; $p = 0.0006$; $I^2 = 95\%$. A leave-one-out sensitivity analysis excluding Mirbastegan et al. (2016) was performed (MD = −4.47 [95% CI −7.27 to −1.66]; $p = 0.002$; $I^2 = 91\%$; total population = 841). A subgroup analysis excluding high-risk-of-bias studies was performed, and a non-significant, although borderline, result was obtained (MD = −3.67 [95% CI −0.74 to −0.04]; $p = 0.05$; $I^2 = 53\%$). A subgroup analysis separately assessing data from studies which investigated high anxiety-inducing situations and data from studies which investigated mild anxiety-inducing situations confirmed a significant result for both subgroups (MD = −5.89 [95% CI −11.64 to −0.14]; $p = 0.04$; $I^2 = 96\%$ and MD = −6.08 [95% CI −10.41 to −1.76]; $p = 0.006$; $I^2 = 92\%$ respectively). A meta-regression was then performed and STAI-S baseline anxiety levels were selected as a moderator (Supplementary Fig. 11), since they represented a continuous variable and they were indicated by the authors of a network meta-regression model as an important moderator (Barić et al., 2018). Results of this meta-regression were not significant ($p_{QM} = 0.4345$; $R^2 = 0.00\%$).

Four trials (Igarashi and Fujita, 2010; Kiani et al., 2016; Mirbastegan et al., 2016; Özkaraman et al., 2018) were included in the fourth meta-analysis, whose purpose was to evaluate the effects of lavender essential oil inhalation on levels of trait anxiety measured with the Spielberger's Trait Anxiety Inventory (STAI-T), compared to no intervention or usual care (Fig. 5). The result of this analysis significantly favored ($p < 0.05$) lavender-based interventions with an effect size of MD = −8.14 [95% CI −14.44 to −1.84]; $p = 0.01$; $I^2 = 91\%$. A leave-one-out sensitivity analysis excluding Mirbastegan et al. (2016) (Mirbastegan et al., 2016) was performed (MD = −4.81 [95% CI −8.32 to −1.31]; $p = 0.007$; $I^2 = 59\%$; total population = 136). A subgroup analysis separately assessing data from studies which investigated high anxiety-inducing situations and data from studies which investigated mild anxiety-inducing situations was not possible in this case due to the limited number of included studies.

Six trials (Hoya et al., 2008; Mirbastegan et al., 2016; Rajai et al., 2016; Seifi et al., 2014; Sgoutas-Emch et al., 2001; Shahnazi et al., 2012) were included in the fifth meta-analysis, evaluating the effects of lavender essential oil inhalation on Systolic Blood Pressure (SBP) values, compared to no intervention or to sham intervention with distilled water or sesame oil (Fig. 6, Supplementary Figs. 1 and 2). One article (Sgoutas-Emch et al., 2001) was included twice in the analysis because it described a trial actually reporting data about couples of different intervention and control groups which could be pooled as if they were two different studies. Since standard deviations of the pre-post mean difference of SBP values in each group were not reported in all included original papers, it was decided to impute the missing change-from-baseline standard deviations with a formula using the correlation coefficient (Higgins and Green, 2011). Unfortunately, no included study reported data in sufficient detail to calculate at least one correlation coefficient which could be also extended to other similar studies. Therefore, it was decided to perform a sensitivity analysis. Three Forest plots were therefore prepared using different correlation coefficients ($r = 0.1$; $r = 0.5$; $r = 0.9$) in order to evaluate whether changing the unknown correlation between pre- and post-test values could affect the overall result of the analysis. When $r = 0.5$, the mean difference was MD = −1.91 mmHg [95% CI −3.32 to − 0.51 mmHg]; $p = 0.008$; $I^2 = 0\%$ (Fig. 6). The result remained significant for a correlation coefficient of $r = 0.1$, in fact, data favored lavender groups in terms of pre-post changes of SBP (MD = −1.94 mmHg [95% CI −3.36 to − 0.51 mmHg]; $p = 0.008$; $I^2 = 0\%$) (Supplementary Fig. 1). The result became non-statistically significant (MD = −2.06 mmHg [95% CI −4.52 to 0.40 mmHg]; $p = 0.1$; $I^2 = 48\%$) when a quasi-linear correlation ($r = 0.9$) was hypothesized between pre- and post-test values (Supplementary Fig. 2). Since it was not possible to estimate the real correlation coefficient, in this case a rule of thumb to consider $r = 0.5$ as the best possible approximation was applied. A leave-one-out sensitivity analysis excluding Mirbastegan et al. (2016) was performed for all meta-analyses associated with the three correlation coefficients but, while for $r = 0.1$ and $r = 0.5$ final results maintained their statistical significance without important differences in p values ($p = 0.006$ and $p = 0.005$, respectively) and no differences in I^2, for $r = 0.9$ the

overall result changed and became significant (MD = −2.79 mmHg [95% CI −5.10 to −0.48]; $p = 0.02$; $I^2 = 31\%$; total population = 338). In this meta-analysis, only one subgroup analysis separately assessing data from studies which investigated high anxiety-inducing situations was possible, since mild anxiety-inducing situations were investigated in one study only (Sgoutas-Emch et al., 2001). This subgroup analysis mirrored the above-described results, being significant for $r = 0.1$ and $r = 0.5$, and non-significant for $r = 0.9$.

Twenty-four trials (Bagheri-Nesami et al., 2017; Bakhsha et al., 2014; Bekhradi and Vakilian, 2016; Bikmoradi et al., 2015; Diego et al., 1998; Hosseini et al., 2016; Hoya et al., 2008; Igarashi and Fujita, 2010; Karadag et al., 2017; Karaman et al., 2016; Kiani et al., 2016; Kianpour et al., 2016; Matsumoto et al., 2017; Mirbastegan et al., 2016; Najafi et al., 2014; Özkaraman et al., 2018; Rajai et al., 2016; Seifi et al., 2014; Şentürk and Tekinsoy Kartın, 2018; Seyyed-Rasooli et al., 2016; Sgoutas-Emch et al., 2001; Shahnazi et al., 2012; Tugut et al., 2017; Uzunçakmak and Ayaz Alkaya, 2018) were included in the sixth meta-analysis, whose purpose was to evaluate the effects of lavender essential oil inhalation on levels of anxiety measured with any validated scale, regardless of comparison type (Fig. 7, Supplementary Figs. 3 and 4). Since standard deviations of the change-from-baseline mean difference of anxiety levels in each group were not reported in the majority of included original papers (Bagheri-Nesami et al., 2017; Bakhsha et al., 2014; Bekhradi and Vakilian, 2016; Diego et al., 1998; Hoya et al., 2008; Igarashi and Fujita, 2010; Karaman et al., 2016; Kianpour et al., 2016; Matsumoto et al., 2017; Mirbastegan et al., 2016; Najafi et al., 2014; Özkaraman et al., 2018; Rajai et al., 2016; Seifi et al., 2014; Sgoutas-Emch et al., 2001; Uzunçakmak and Ayaz Alkaya, 2018), it was decided to perform a sensitivity analysis. Among these trials, when the study design was similar enough to one of the other six included studies which reported data in sufficient detail (Bikmoradi et al., 2015; Hosseini et al., 2016; Karadag et al., 2017; Kiani et al., 2016; Seyyed-Rasooli et al., 2016; Shahnazi et al., 2012), the correlation coefficient was calculated from the study reported in detail, and then applied to the study with a similar design but lacking details in regard to change-

from-baseline standard deviations for their calculation (Higgins and Green, 2011). For the sensitivity analysis, three forest plots were prepared using different correlation coefficients ($r = 0.1$; $r = 0.5$; $r = 0.9$) in order to evaluate whether changing the unknown correlation between pre- and post-test values in the remaining studies could affect the overall result of the analysis. When $r = 0.5$, the obtained standardized mean difference was Hedges's $g = -0.73$ [95% CI −1.00 to −0.46]; $p < 0.00001$; $I^2 = 85\%$, thus indicating a significant effect size of studied intervention (Fig. 7). The result remained statistically significant ($p < 0.00001$), favoring lavender groups, even when almost no correlation ($r = 0.1$) (Supplementary Fig. 3) or when a quasi-linear correlation ($r = 0.9$) (Supplementary Fig. 4) were applied. Even in this case it was assumed that the best possible approximation for those studies without sufficient reported detail was $r = 0.5$. A subgroup analysis separately assessing data from studies which investigated high anxiety-inducing situations and data from studies which investigated mild anxiety-inducing situations confirmed a significant result for trials with patients involved in high anxiety-inducing situations (Hedges's $g = -0.83$ [95% CI −1.11 to −0.56]; $p < 0.00001$; $I^2 = 78\%$) and, interestingly, when outliers were removed from the subgroup analysis, heterogeneity significantly dropped (Hedges's $g = -0.67$ [95% CI −0.86 to −0.47]; $p < 0.00001$; $I^2 = 55\%$). However, results of the subgroup analysis of studies which investigated mild anxiety-inducing situations were non-significant. A meta-regression of studies included in this meta-analysis (effects of lavender inhalation on anxiety measured with any validated scale) was performed with the setting type and the duration of lavender administration as moderators (Supplementary Fig. 11). Settings were grouped as follows: day-hospital setting (e.g.: dialysis or chemotherapy centers), non-health facility (e.g.: university, school), intensive hospitalization setting (e.g.: ICU, burns unit), waiting for an invasive procedure in a health facility (e.g.: endoscopy, surgery, device insertion), and gynecological setting. The duration of lavender administration was categorized as single- or multi-dose, when one single administration or multiple administrations over a period of days were provided respectively. Results of this meta-regression model were significant (Test of Moderators $p_{QM} = 0.0013$) and can justify up to 51.49% of the pooled estimate heterogeneity. Conditional number K resulted equal to 13, which is well below the

threshold of 30, used as a rule-of-thumb to identify a moderate risk of collinearity (and also below the stricter threshold of 15). Therefore, we can consider the model at low risk of collinearity. The robustness of such model was further tested by a permutation test (1000 interactions), which displayed a significant result ($p = 0.0330$). Six trials (Ayik and Özden, 2018; Azima et al., 2015a; Bahrami et al., 2017; Effati-Daryani et al., 2015; Lamadah and Nomani, 2016; Seyyed-Rasooli et al., 2016) were included in the seventh meta-analysis, whose purpose was to evaluate the effects of lavender essential oil massage on levels of anxiety measured with any validated scale (including the Spielberger's State and Trait Inventory or STAI), compared to other physical therapies (reflexology or massage without oil) or usual care (Fig. 8). The result of this analysis significantly favored ($p < 0.05$) lavender-based interventions with an effect size of Hedges's $g = -0.66$ [95% CI −0.97 to −0.35]; $p < 0.0001$; $I^2 = 61\%$. In this meta-analysis, only one subgroup analysis separately assessing data from studies which investigated high anxiety-inducing situations was possible, since mild anxiety-inducing situations were investigated in two studies only (Azima et al., 2015a; Effati-Daryani et al., 2015). Results of this subgroup analysis were significant and showed a greater size effect (Hedges's $g = -0.77$ [95% CI −1.14 to −0.41]; $p < 0.0001$; $I^2 = 56\%$).

Risk of bias across studies

Funnel plots regarding the third (Fig. 9) and the sixth meta-analyses (Fig. 10) visually showed some mild degree of asymmetry, which diminished when the outlying trial (Mirbastegan et al., 2016) was excluded, and visually turned into high symmetry when all RCTs characterized by high risk of bias were excluded (Supplementary Fig. 5).

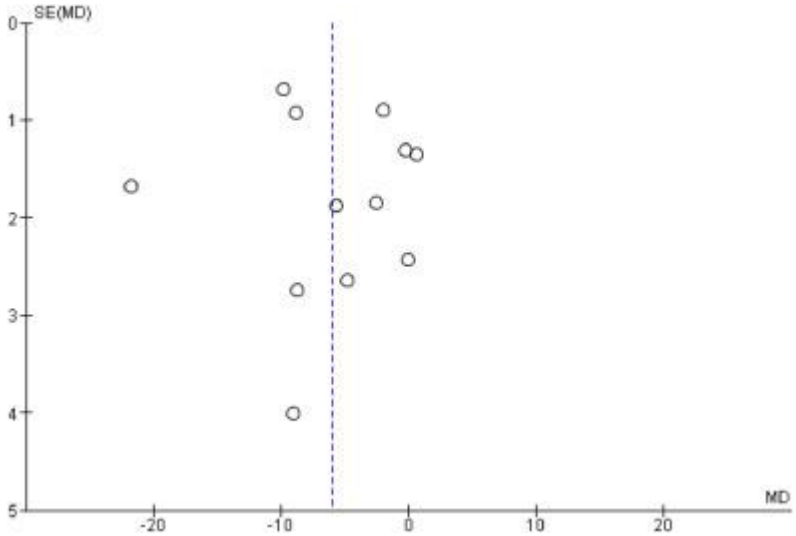

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Fig. 9. Funnel plot referred to the third meta-analysis (Inhalation, STAI-S) (Fig. 4).

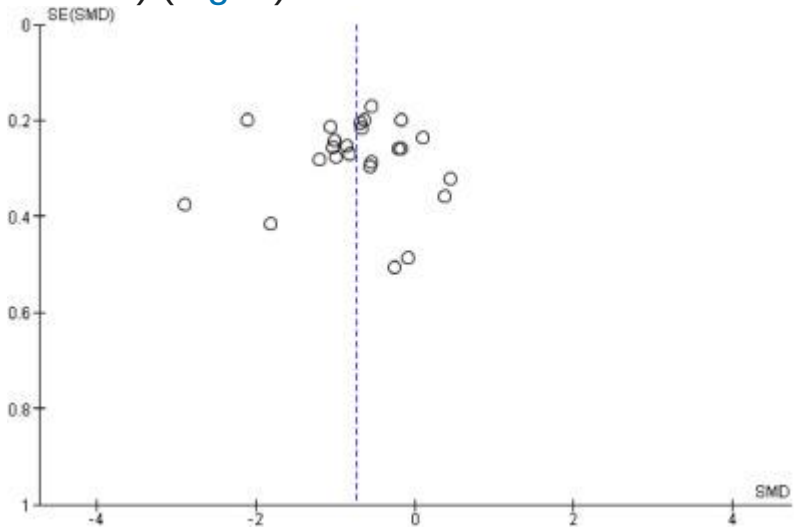

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Fig. 10. Funnel plot referred to the sixth meta-analysis (Inhalation, any validated anxiety questionnaire, any comparison type) (Fig. 7).

When performing the Egger's test for the third meta-analysis (inhalatory lavender with STAI-S as an outcome measure) without excluding any trial (Fig. 9), the following results were obtained: intercept = 1.115 [95% CI −4.46 to 6.69]; $p = 0.7$. When performing the Egger's test for the sixth meta-analysis (inhalatory lavender with any validated anxiety assessment tool as an outcome measure) without excluding any trial (Fig. 10), the following results were obtained: intercept = 0.181 [95% CI −4.09 to 4.45]; $p = 0.9$. In both cases, the null hypothesis that the intercept is not significantly

different from zero was confirmed, and, therefore, we cannot affirm that publication bias is present.
When performing the p-curve test for significant meta-analyses, the following results were obtained: in the first meta-analysis (Silexan®, HAM-A) (Supplementary Fig. 6), a right skewed p-curve was observed ($p < 0.0001$), with a power estimate of 92% (CI: 64%, 99%) and a non-significant test for flatness ($p = 0.9967$). In the third meta-analysis (Inhalation, STAI-S) (Supplementary Fig. 7), a right skewed p-curve was observed ($p < 0.0001$), with a power estimate of 99% (CI: 99%, 99%) and a non-significant test for flatness ($p = 0.9999$). In the fourth meta-analysis (Inhalation, STAI-T) (Supplementary Fig. 10), a right skewed p-curve was observed ($p = 0.004$), with a power estimate of 82% (CI: 27%, 98%) and a non-significant test for flatness ($p = 0.93$). In the sixth meta-analysis (Inhalation, any validated anxiety questionnaire) (Supplementary Fig. 8), a right skewed p-curve was observed ($p < 0.0001$), with a power estimate of 99% (CI: 88%, 99%) and a non-significant test for flatness ($p = 0.9999$). In the seventh meta-analysis (Massage, any validated anxiety questionnaire) (Supplementary Fig. 9), a right skewed p-curve was observed ($p < 0.0001$), with a power estimate of 96% (CI: 80%, 99%) and a non-significant test for flatness ($p = 0.9997$). These results indicate that the first (Silexan, HAM-A) (Fig. 2), third (Inhalation, STAI-S) (Fig. 4), sixth (Fig. 7) (Inhalation, any validated anxiety questionnaire) and seventh (Fig. 8) (Massage, any validated anxiety questionnaire) meta-analyses are free of publication bias due to selective reporting or “p-hacking”, thus having evidential value. P-curve test results were not used to calculate the magnitude of the true effect size of meta-analyses since this method is considered valid only if I^2 is below 50% (Simonsohn et al., 2014a).

Discussion

In this systematic review and meta-analysis, the effects of lavender (administered in any way and formulation) on anxiety were analyzed on the basis of published evidence on the topic. 65 RCTs and 25 NRSs were included in the qualitative synthesis and 37 RCTs were included in the quantitative synthesis. Methodological quality of included RCTs was evaluated with the Cochrane risk-of-bias tool, and results of this assessment showed that the overall

quality of available evidence is low, with around 89% of included RCTs characterized by a high risk of bias. It should be highlighted that the majority of included studies regarded inhalation or aromatherapy interventions, and this determined an underestimation of their overall quality, since lavender odor is not concealable and performance bias is therefore very difficult to avoid. Considering performance bias as a non-key domain, the overall quality ameliorated, with around 71% of included RCTs characterized by an overall high risk of bias. In the qualitative synthesis, evidence was retrieved from both RCTs and NRSs in order to provide a broad and complete overview about how lavender has been tested to date from a clinical point of view. The qualitative synthesis shows that, when considering study population, pediatric subjects are under-represented, therefore most available evidence actually regards adult and elderly individuals. It is also important to report that, in the majority of included studies, lavender was administered through inhalation and aromatherapy, due to the fact that this route of administration is easy to deliver, inexpensive, safe, and non-invasive.
Overall, the qualitative synthesis indicates that 54 out of 65 included RCTs reported at least a significant result in favor of lavender use for anxiety, either as a significant improvement from baseline within intervention groups, or as a significant post-test amelioration of anxiety levels in intervention groups compared to control groups. 17 out of 25 included NRSs reported a significant improvement in at least one outcome (anxiety) measure within intervention groups, or a significant post-test difference between intervention and control (when present) groups in favor of lavender use.

From a quantitative point of view, seven meta-analyses were performed, trying to achieve the highest possible homogeneity across characteristics of included studies, in order to obtain information which could be useful to make decisions in clinical practice.

Efficacy of orally administered Silexan® on anxiety levels

Silexan® is a capsule preparation of essential oil of lavender titrated to 35% of linalool and linalyl acetate.

Results of the first meta-analysis (Fig. 2) demonstrated a significant effect of orally administered Silexan® (80 mg) compared to placebo in terms of reduction of anxiety levels measured with the Hamilton's Anxiety Rating Scale (HAMA), as a result of a long-term treatment period (over two months) with studied remedy which was taken by patients on a daily basis (once every day). This meta-analysis is characterized by a high level of homogeneity in terms of study design, given that all included trials (5 RCTs with a total of 1173 participants) were conducted by the same research team. In fact, homogeneity was found across these trials when considering study population (patients with mild-to-severe anxiety disorder), intervention and control type, trial duration, sampling time, and outcome measure. Despite missing data about change-from-baseline standard deviations with regard to anxiety levels in one study (Kasper et al., 2015), thanks to the above mentioned homogeneity it was possible to impute the correlation coefficient between pre- and post-test values
from Kasper et al. (2010) (Kasper et al., 2010). The measure of calculated statistical heterogeneity was high (I^2 = 74%) and this result was unexpected considering the overall homogeneity of study designs. However, when removing Kasper et al. (2010) from the analysis, I^2 dropped to 28%. It is possible that this was caused by the characteristics of study population, that was relatively different from other trials (patients with subsyndromal anxiety). Another interesting point regards Kasper et al., 2017 (trial A), which is the study with the smallest effect size: this may be explained by the fact that the control group in this trial was given a placebo capsule per day scented with 0.08 mg of lavender oil, a feature that may have implied an anxiolytic effect (also in the light of our findings about lavender inhalation). It is also important to underscore that, among these studies, three of them had a high overall risk of bias (Kasper et al., 2017, 2016, 2015), another one had a low risk of bias (Kasper et al., 2010), while the remaining one had an unclear risk of bias (Kasper et al., 2014) (in these cases performance bias was considered a key domain since lavender or placebo were administered in capsules). Since included trials shared the same methodology and were conducted by the same research team, the absence of studies performed by other researchers might cover possible biases. However, the p-curve test (Supplementary Fig. 6) showed that this meta-analysis was not flawed by publication bias,

ruling out selective reporting or “p-hacking” as an explanation for the significant findings.

The second meta-analysis (Fig. 3) still investigated the efficacy of Silexan® (80-mg capsules, orally administered once a day for more than one month) compared to placebo on anxiety measured with the Zung Self-Rating Anxiety Scale (Zung-SAS). Even in this case, the meta-analysis showed a significant effect of intervention on the reduction of anxiety levels. Moreover, the level of statistical heterogeneity was low (I^2 = 17%). Unfortunately, only three studies were included in this analysis (with a total of 451 participants), two of which also comprised in the first meta-analysis and performed by the same research team (Kasper et al., 2015, 2010). However, in this case there was also a third trial conducted by other researchers (Woelk and Schläfke, 2010). Among these RCTs, two of them were characterized by a high overall risk of bias (Kasper et al., 2015; Woelk and Schläfke, 2010), whereas the remaining one had a low overall risk of bias (Kasper et al., 2010). Even in this second meta-analysis a high level of homogeneity across characteristics of included studies was found, especially in terms of study population, intervention and control type, trial duration, sampling time, and outcome measurement.

Overall, it is possible to underscore that these results clearly indicate the possible efficacy of Silexan® in reducing anxiety levels during a long-term treatment, although the relative scarcity of high-quality RCTs with a low overall risk of bias prevents from drawing firm conclusions. Therefore, it is plausible that the oral administration of a standardized formulation titered to linalool and linalyl acetate like Silexan® could be useful for anxiety treatment, even thanks to its safety and tolerability profile, as well as to the possibility to be a potential integrative therapy in adjunct to the administration of anxiolytic drugs. A PET- and MRI-based RCT from Baldinger et al. (2015) suggested that Silexan®, administered daily at the dose of 160 mg for a minimum of 8 weeks, can induce, compared to placebo, a reduction of 5-HT1A receptor binding in healthy subjects over a period of several weeks. This finding is in line with a general mechanism of action shared by anxiolytic and antidepressant drugs like SSRIs, which mainly induce changes in 5-HT1A receptor expression or affinity (Baldinger et al., 2015). Despite this, further high-quality RCTs are needed to confirm these results, possibly conducted by different research teams.

Efficacy of lavender essential oil inhalation on anxiety levels

Inhalation of lavender essential oil is very easy to put into practice, and, for this reason, there are many studies investigating the efficacy of this way of administration. In the third and fourth meta-analysis, it was studied the efficacy of inhalatory administered lavender oil compared to no intervention or usual care on anxiety levels measured with the Spielberger's State-Trait Anxiety Inventory (STAI). As previously mentioned, the STAI can be divided into two questionnaires, one of them focused on state anxiety (STAI-S), whose questions are referred to the specific moment in which they are asked, and the other one focused on trait anxiety (STAI-T), namely the “baseline” level of anxiety that the patient usually experiences. In included studies, inhalation of lavender followed a preparation procedure characterized by putting some drops of essential oil on a neutral support (a cotton wad or a handkerchief) which was then smelled for a certain amount of time (varying from 2 to 30 min), once or multiple times every day, for one up to many days (even a few months).

In the third meta-analysis, focused on STAI-S, or state anxiety, 12 trials were included (Cruz et al., 2012; Hosseini et al., 2016; Igarashi and Fujita, 2010; Kavurmacı et al., 2015; Kiani et al., 2016; Mirbastegan et al., 2016; Najafi et al., 2014; Özkaraman et al., 2018; Seifi et al., 2014; Seyyed-Rasooli et al., 2016; Shahnazi et al., 2012; Tugut et al., 2017) with a total of 901 participants. Results of this meta-analysis (Fig. 4) showed a significant efficacy of lavender essential oil inhalation in the reduction of state anxiety. It has to be underscored that the heterogeneity of this analysis was high ($I^2 = 95\%$).
After visually assessing the forest plot (Fig. 7) and the corresponding funnel plot (Fig. 9), all potential outliers were checked with a detection analysis for their precise identification, and (Mirbastegan et al., 2016) tested positive, thus being recognized as an outlier.
When a sensitivity analysis excluding this trial was performed (MD = −4.47 [95% CI −7.27 to −1.66]; $p = 0.002$; $I^2 = 91\%$), the result remained significant with a modest reduction of the effect size. However, the level of heterogeneity, although diminishing, still remained high, probably suggesting the presence of an unknown moderator of the effect. The outlier result

of Mirbastegan et al. (2016) was due to the fact that patients (admitted to an Intensive Care Unit for myocardial infarction) in the control group experienced a marked worsening of anxiety levels, in parallel with an improvement in the intervention group. It is possible to hypothesize that, among patients (hospitalized in an Intensive Care Unit which is anxiogenic by itself), intervention elicited placebo effects due to its association with the perception of lavender smell, whereas in the control group, who received a simple manipulation without any characteristic sensory stimulus (cotton wad with water drops), nocebo effects occurred.

The high level of statistical heterogeneity across studies included in this meta-analysis might be explained by anxiety baseline levels, their different study populations (varying from university students to patients hospitalized in an intensive care ward), and by their various specific procedures of inhalation (it proves more difficult to standardize the administration of inhalation therapy in respect of taking a single capsule with a precise amount of drug). Finally, among the twelve included studies, five of them (Cruz et al., 2012; Igarashi and Fujita, 2010; Kiani et al., 2016; Mirbastegan et al., 2016; Tugut et al., 2017) reported a high overall risk of bias, in this case evaluated without considering performance bias as a key domain due to the difficulty of concealing the administration of studied intervention (lavender-based inhalatory treatment). When a subgroup analysis excluding the previously mentioned high-risk-of-bias studies was performed, a non-significant, although borderline, result was obtained (MD = −3.67 [95% CI −0.74 to −0.04]; $p = 0.05$; $I^2 = 53\%$). A confirmatory test conducted with R reported a slightly more significant result ($p = 0.045$).

Results of the meta-regression investigating anxiety baseline levels as a moderator of the effect were non-significant, therefore we cannot affirm that, in the sample of analyzed studies, baseline anxiety levels can influence observed variability nor can partially justify the heterogeneity. Therefore, even if previous studies individuated in anxiety baseline levels a moderator of the anxiolytic effect (thus giving to such levels a priority as a possible moderator over other variables), in our analysis we cannot confirm the same result. This may be explained by the fact that all included studies in the meta-regression involved patients with moderate-to-severe baseline anxiety levels (STAI-S). Other moderators were not

studied due to the limited number of studies and following the parsimony criteria to avoid spurious findings, therefore for this pooled estimate no quantitative explanations for the heterogeneity were found.

The fourth meta-analysis was focused on the STAI-T, assessing trait anxiety, and included four studies (Igarashi and Fujita, 2010; Kiani et al., 2016; Mirbastegan et al., 2016; Özkaraman et al., 2018), already comprised in the previous analysis, with a total of 196 participants. Results of this analysis (Fig. 5) reported a significant efficacy of lavender essential oil inhalation for the reduction of trait anxiety, that is the patient's habitual anxiety. Even in this case, caution is needed in interpreting obtained results due to a high risk of bias characterizing three out of four included trials (Igarashi and Fujita, 2010; Kiani et al., 2016; Mirbastegan et al., 2016), and a high level of heterogeneity across studies (I^2 = 91%), which can be partially explained by the above mentioned reasons for the analysis about STAI-S (Fig. 4). It is interesting to notice that, even in this case, when performing an outlier-detection analysis, the trial conducted by Mirbastegan et al. (2016) still appears as the only outlier, and, after excluding it from the analysis, the level of heterogeneity drops to a much lower value (I^2 = 59%), which could be considered acceptable if the variability of the settings of included studies is adequately taken into account. Moreover, results of subgroup analyses separately assessing data from studies investigating high and mild anxiety-inducing situations showed an independently significant effect in favor of lavender use, thus indicating that lavender inhalation may be effective to improve STAI scores both in high and in mild anxiety-inducing situations. In both the third and fourth meta-analyses, the p-curve test (Supplementary Figs. 7 and 10) showed that these meta-analyses did not suffer from publication bias, thus ruling out selective reporting or “p hacking” as an explanation for these significant findings.
Considering the results of these two meta-analyses (Figs. 4 and 5), it is possible to assume that inhaling lavender essential oil might be effective in diminishing state and trait anxiety levels, although this finding must be considered as exploratory and firm conclusions cannot be driven due to the overall risk of bias of included studies.

The fifth meta-analysis (Fig. 6) aimed to investigate the effects of lavender essential oil inhalation (compared to no or sham intervention) on an anxiety-related physiological parameter like systolic blood pressure. Six studied were included (Hoya et al., 2008; Mirbastegan et al., 2016; Rajai et al., 2016; Seifi et al., 2014; Sgoutas-Emch et al., 2001; Shahnazi et al., 2012) with a total of 398 participants. Results of this meta-analysis appeared significant when either no correlation ($r = 0.1$) or an intermediate correlation coefficient ($r = 0.5$) were hypothesized between pre- and post-test values, with the lowest possible level of heterogeneity ($I^2 = 0\%$). On the other hand, results were not significant when a quasi-linear correlation was applied ($r = 0.9$). Additionally, it should be considered that, in the first two sub-analyses (when $r = 0.1$ or $r = 0.5$), there was a trial (Shahnazi et al., 2012) which accounted for a relatively high and disproportionated weight (>70%) with respect to other studies, and such weight was just downsized in the third sub-analysis only (when $r = 0.9$). However, a leave-one-out sensitivity analysis excluding the same outlier mentioned before (Mirbastegan et al., 2016), showed a change in the result, which became significant under this condition ($p = 0.02$; $I^2 = 31\%$). Since all included studies were at high risk of bias except for Shahnazi et al. (2012), results of this meta-analysis impede from taking any position in favor of the efficacy of lavender essential oil inhalation on an anxiety-related physiological parameter like systolic blood pressure. However, these results do not exclude that some degree of efficacy could be present, which might become the subject of further research on the topic. It has to be noticed that the majority of the studies included in this meta-analysis investigated high anxiety-inducing situations, and that the subgroup analysis confirmed a significant effect.

In the sixth meta-analysis, it was decided to extend the sample of meta-analyzable studies renouncing to a strict homogeneity for outcome measure, thus including each trial in which any validated anxiety scale was used, and therefore adopting the standardized mean difference as a measure of effect size (Fig. 7). This analysis was performed with the purpose to evaluate whether it was still possible to obtain a significant result in favor of lavender use even when applying less strict criteria for trial inclusion in the meta-analysis. Twenty-four studies were therefore included (Bagheri-Nesami et al., 2017; Bakhsha et al., 2014; Bekhradi and

Vakilian, 2016; Bikmoradi et al., 2015; Diego et al., 1998; Hosseini et al., 2016; Hoya et al., 2008; Igarashi and Fujita, 2010; Karadag et al., 2017; Karaman et al., 2016; Kiani et al., 2016; Kianpour et al., 2016; Matsumoto et al., 2017; Mirbastegan et al., 2016; Najafi et al., 2014; Özkaraman et al., 2018; Rajai et al., 2016; Seifi et al., 2014; Şentürk and Tekinsoy Kartın, 2018; Seyyed-Rasooli et al., 2016; Sgoutas-Emch et al., 2001; Shahnazi et al., 2012; Tugut et al., 2017; Uzunçakmak and Ayaz Alkaya, 2018), with a total of 1682 participants. Results of this meta-analysis were markedly significant ($p < 0.00001$) in support of lavender-based interventions, regardless of the value attributed to the correlation coefficient in the sensitivity analysis, as previously described in detail. Although it can be underscored that there was a high level of heterogeneity across studies ($I^2 = 85\%$), if the outlying trials conducted by Mirbastegan et al. (2016), Senturk et al. (2018) and Tugut et al. (2017) (Mirbastegan et al., 2016; Şentürk and Tekinsoy Kartın, 2018; Tugut et al., 2017) (identified through an outlier-detection analysis) were excluded from the analysis, the level of heterogeneity went down to $I^2 = 65\%$ and the overall effect size, although reduced ($g = -0.54$ [−0.73; −0.36]), still remained significant ($p < 0.00001$). Moreover, if we consider the heterogeneity across study designs of included trials in terms of study populations, settings, procedures to administer lavender essential oil inhalation, sampling time, and psychometric scales used to measure anxiety, which may act as moderators of the effect, then a higher level of heterogeneity can be acceptable.
It is necessary to underscore the relative abundance (17 out of 24) of studies characterized by high risk of bias (Bagheri-Nesami et al., 2017; Bakhsha et al., 2014; Bekhradi and Vakilian, 2016; Diego et al., 1998; Hoya et al., 2008; Igarashi and Fujita, 2010; Karadag et al., 2017; Kiani et al., 2016; Kianpour et al., 2016; Matsumoto et al., 2017; Mirbastegan et al., 2016; Rajai et al., 2016; Seifi et al., 2014; Şentürk and Tekinsoy Kartın, 2018; Sgoutas-Emch et al., 2001; Tugut et al., 2017; Uzunçakmak and Ayaz Alkaya, 2018). Therefore, in order to test the consistency of results, a subgroup analysis was performed, excluding the above mentioned trials at high risk of bias. Results of the sixth meta-analysis were confirmed in this specific subgroup analysis involving 535 participants (Hedges's $g = -0.64$ [95% CI

−0.82 to −0.47]; $p < 0.00001$; $I^2 = 0\%$), with a marked reduction of the level of heterogeneity and a homogeneous relative weight of each included study. Interestingly, a subgroup analysis with an acceptable statistical heterogeneity (Hedges's $g = -0.67$ [95% CI −0.86 to −0.47]; $p < 0.00001$; $I^2 = 55\%$) showed that lavender inhalation performed particularly well in reducing anxiety in high anxiety-inducing situations like ICUs, hemodialysis, open heart surgery, etc.
To better identify the sources of heterogeneity, a meta-regression (see Supplementary Fig. 11 for details) was performed, investigating the different situations and different treatment duration as moderators of the effects, and the results of this meta-regression explained an important percentage of heterogeneity ($R^2 = 51.49\%$, $p = 0.0013$). Therefore, different situations and different duration over time (single- or multi-dose) of the administration of lavender scent are probably moderators of the effect. This finding is important because, on the one hand, it supports the idea that lavender inhalation can be effective, whereas, on the other hand, it suggests the importance of paying attention to these two moderators when planning future trials.
In this meta-analysis, the p-curve test (Supplementary Fig. 8) was conducted using the subset of studies excluding outliers, and did not show any publication bias, ruling out selective reporting or “p-hacking” as an explanation for the significant findings.

In the light of results of this last meta-analysis and of the previous ones, keeping in mind reported limitations and considering that lavender essential oil inhalation is a very easy intervention to put into practice, also characterized by low costs, high sustainability, good safety profile, and no training to be administered, it is possible to suggest that this treatment may be considered by clinicians in their practice. In particular, lavender essential oil inhalation could be used as an integrative treatment for chronic care of anxiety, or by itself as an acute treatment for those situations associated with mild levels of anxiety, or as a help in situational anxiety.

Efficacy of massage with lavender essential oil on anxiety levels

The seventh (and last) meta-analysis (Fig. 8) investigated the effects of massage with lavender essential oil on anxiety levels if compared to other physical therapies (reflexology or massage with

or without other oils) or to usual care. In this analysis, six RCTs were included, involving 448 participants (Ayik and Özden, 2018; Azima et al., 2015a; Bahrami et al., 2017; Effati-Daryani et al., 2015; Lamadah and Nomani, 2016; Seyyed-Rasooli et al., 2016). The result of this analysis significantly favored ($p < 0.001$) lavender-based interventions with an effect size of Hedges's $g = -0.66$ [95% CI −0.97 to −0.35]; $p < 0.0001$; $I^2 = 61\%$, and the subgroup analysis confirmed this effect in high anxiety-inducing situations. Even in this case, it is important to report that three out of six studies were characterized by low quality due to their high risk of bias, although the p-curve test did not show any publication bias (and “p-hacking”, likely), ruling out selective reporting or “p-hacking” as an explanation for the significant findings (Supplementary Fig. 9). The result of this meta-analysis, although encouraging, needs to be interpreted with caution both because of the overall quality of included trials, and because of the difficulty to isolate the specific beneficial effect of lavender essential oil from the action of massage.

Limitations

The most important limitation of this review is the low average quality of studies on this topic. The majority of RCTs included in the qualitative synthesis were characterized by a high overall risk of bias. A first consideration regards performance bias: when using lavender essential oil, it proves difficult to properly blind patients and investigators to its peculiar smell, and, apart from specific conditions like the oral administration of Silexan® in which the essential oil was encapsulated with jelly (and, therefore, lavender odor was less perceivable), other studies used ways of administration that made impossible (or even nonsense in the case of inhalation) to conceal the smell of lavender. However, even when performance bias was not considered as a key domain due to the aforementioned reason, the prevalence of high-risk-of-bias studies remained high, mostly indicating an average poor methodological awareness (or loose compliance to study reporting standards) among researchers who investigated lavender.

Another important limitation regards the heterogeneity of the design of studies which investigated the efficacy of lavender for anxiety, especially with regard to non-oral ways of administration such as

inhalation or massage. It would be advisable to reach a consensus in order to standardize study designs and to possibly achieve the best level of evidence even from small-to-middle sized clinical trials. The most frequently outcome measure which was used across included studies was the Spielberger's State-Trait Anxiety Inventory (STAI), composed of two questionnaires with 20 items each (one questionnaire assessing state anxiety, the other one evaluating trait anxiety). It was noticed that, in some studies, the correct use of each of the two questionnaires for anxiety assessment was possibly misinterpreted. Moreover, it was not always clear which one of the two questionnaires was employed by investigators, thus making it difficult to assess the appropriateness of study outcome assessment and introducing an additional potential source of bias.

Conclusions

In conclusion, the oral administration of lavender essential oil, standardized and titrated to linalool and linalyl acetate concentrations (like Silexan®), seems to have a promising efficacy in the treatment of anxiety, although further high-quality RCTs are needed to confirm these findings, possibly investigating lavender essential oil in the form of a medicinal product. The administration of lavender essential oil through inhalation seems effective in the reduction of anxiety levels, and, in particular, its simplicity, safety, and low cost make it a therapeutic option which may be considered in certain clinical contexts. However, even in this case, it would be recommended to confirm these findings with further high-quality RCTs, considering the heterogeneity of available data and high prevalence of high risk-of-bias trials, although the efficacy of lavender seems to be confirmed even when low-quality studies are excluded from the analysis, and additional analyses seem to confirm the reliability of this finding. Lavender essential oil administered through massage appears effective, but available studies are not sufficient to determine with certainty whether the benefit is due to a specific effect of lavender, thus impeding from clearly differentiating it from the beneficial effect of massage. Other ways of administration do not have enough data (or no data at all, like the sublingual route of administration) in their support to draw any conclusion. Proportionally, only a limited percentage of studies report data about safety of lavender-based interventions, but

available information essentially outlines a safe profile without severe adverse effects. It is advisable that further high-quality trials are conducted trying to make study designs more homogeneous, and that more attention should be paid to safety data collecting and reporting.

Declaration of Competing Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix. Supplementary materials

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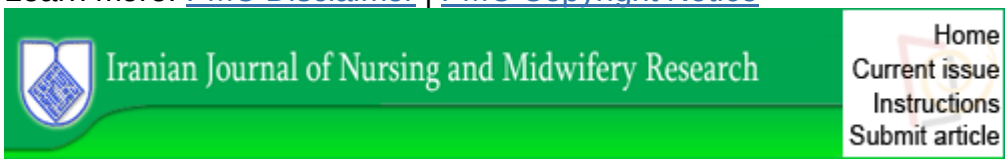

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Effect of lavender scent inhalation on prevention of stress, anxiety and depression in the postpartum period

Maryam Kianpour,[1] Akram Mansouri,[1] Tayebeh Mehrabi,[2] and Gholamreza Asghari[3]

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Go to:

Abstract

Background:

Stress, anxiety, and postpartum depression are the most common problems among women in their childbearing age. Research has shown that aromatherapy administered during labor reduces anxiety in mothers. With regard to the specific biological conditions in postpartum period and the subsequent drop in hormone levels, this study investigated the effect of lavender on prevention of stress, anxiety, and postpartum depression in women.

Materials and Methods:

In a clinical trial, 140 women admitted to the obstetric and gynecological unit were randomly divided into aromatherapy and non-aromatherapy groups immediately after delivery. Intervention with aromatherapy consisted of inhaling three drops of lavender essential oil every 8 h with for 4 weeks. The control group received routine care after discharge and was followed up by telephone only. After 2 weeks, 1 and 3 months of delivery, women were assessed by the 21-item Depression, Anxiety, and Stress Scale and the Edinburgh stress, anxiety, and depression scale in the two groups. Data analysis was performed by Mann-Whitney, analysis of variance (ANOVA), and post hoc tests. Level of significance was set as 0.05 for all tests.

Results:

The results showed that the mean stress, anxiety, and depression at time point of 2 weeks ($P = 0.012$, $P < 0.0001$, and $P = 0.003$, respectively) and stress, anxiety, and depression scores at time points of 1 month ($P < 0.0001$) and 3 months after delivery ($P < 0.0001$) were significantly lower in the study group compared with the control group.

Conclusions:

Inhaling the scent of lavender for 4 weeks can prevent stress, anxiety, and depression after childbirth.

Keywords: Anxiety, depression, lavender, postpartum period, prevention, scent of lavender, stress

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INTRODUCTION

Pregnancy and delivery are pleasant physiological phenomena, but at times, changes occur in pregnant women's mood that make them so sensitive to psychological stimulants and lead to their mental problems. [1,2] After delivery, women start losing self-control on the events and feel helpless, and are involved in confusion and manifest signs such as depression, anxiety, and posttraumatic stress disorder. [3] Modares *et al*. reported the prevalence of stress disorder as 20%, while after a traumatic delivery, it was 37.7%. [4] Post delivery anxiety influences 5-20% of the mothers. [5] Eventually Postpartum depression (with a variant prevalence of 5-40% in different societies) accounts for 12.5% of the women's hospital admissions due to psychological problems. [6] Postpartum depression is among the most important complications of postpartum stress, which increases mothers' and infants' vulnerability. [4] Stress can lead to anxiety which is a mental reaction to a real or mentally made threat. Lack of sleep, poor nutrition, high consumption of caffeine, smoking, and physical diseases are among the manifestations of anxiety. [7] Anxiety in mothers decreases oxytocin secretion and milk production. A study in Japan showed that postpartum anxiety and depression led to lower self-confidence and, consequently, decreased breast feeding. [8] Although minor anxiety can somehow encourage the individuals to take charge of their responsibility properly or to learn how to modify their lifestyle and habits, severe anxiety can be very disabling. Anxiety increasing as much as a panic disorder can cause disability. [9] Postpartum depression can have negative effects on mothers' role and, in some cases, impair maternal interest to infant and family members. As birth is considered a pleasant event, mothers' mental suffering can be very confusing for the family members. It also negatively affects their sexual desire and, consequently, their marital relationship. Postpartum depression is a major health problem that impairs healthy mother-infant relationship. [10] If not treated, depression gradually subsides normally 6 months after delivery, while a longer period of time increases the number of complications and their severity. [11] The first step in treatment of such disorders is

prevention. Recent studies show that treatment interventions before and after delivery act very successfully in reduction of risk among the women with severe delivery-related disorders.

Preventive treatments during delivery and immediately after that include supportive psychotherapy, interpersonal psychotherapy, and medication. Prophylactic medication is recommended for high-risk mothers immediately after delivery. [12] Since use of psychotropic drugs by breast feeding mothers causes problems such as severe drowsiness and diminished response of mothers to the cries of infants during sleep, changes in sexual function, fatigue, changes in role, confusion, hypotension, tachycardia, etc., and also due to their tranquilizing effect on the infant through the milk they receive, these medications are limited during breast feeding. [13] Research shows that one of the existing treatments to reduce stress, anxiety, and depression is aromatherapy. [14,15] Sahebalzamin *et al*. reported that aromatherapy inhalation of lavender and rose essence combination significantly decreased the level of anxiety and depression among the students residing in hostels. [9] A significant decrease in cortisol release from the adrenal gland, a significant increase in secretion of serotonin from the digestive system, and a significant reduction of anxiety during delivery have been all reported after inhalation of lavender in Mirzaei *et al*. 's study. [16] Pemberton and Turpin reported the effect of lavender and sage on the reduction of stress resulting from working in ICU among the nurses. [17] There are some studies on aromatherapy in postpartum period, including Imura *et al*. in which mothers' and infants' physical and mental status improvement and facilitation of mother-infant interaction have been reported. [18] Conrad and Adams conducted a comparative study on the effects of inhalation and massage aromatherapy using a combination of lavender rose essentials and reported that both methods significantly reduced depression and anxiety although massage aromatherapy was more effective. [15] One of the scented essential oils used in aromatherapy is lavender oil. Its scientific name

is Lavandula angustifolia from the group of mints with the English name of lavender. Among the effective ingredients is a combination of linalool and linalyl acetate. Linalool acts as a tranquilizer by affecting aminobutyric acid receptors in the central nervous system. [19] Oil essence of this plant contains phenol aldehyde or alcohol with the highest germicidal effect. [20] With regard to the high prevalence of stress, anxiety, and postpartum depression and lack of adequate research on the effect of inhalation aromatherapy on prevention of stress, anxiety, and postpartum depression, the present study aimed to investigate the effect of lavender on the prevention of stress, anxiety, and postpartum depression in women.

Go to:

Materials and Methods

This is a clinical trial (No. 392556) that was conducted after obtaining permission from the ethics committee of Isfahan and Lorestan universities of medical sciences. In this study (2014), 171 women hospitalized in the midwifery and gynecology ward of Charity Hospital of Asali in Khorramabad, Iran were selected through convenient sampling based on the inclusion criteria after delivery and they were explained about Golkaran the goals of study and asked to sign a written consent form. Inclusion criteria were being literate, having Iranian nationality, a single tone pregnancy, termination of pregnancy between 37 and 42 weeks of gestational age, birth of a healthy infant, no postpartum complications such as acute hemorrhage and infection, no maternal problems such as preeclampsia during their current pregnancy, no congenital abnormality in infants or not being hospitalized in ICU, no drugs or alcohol consumption by the mother, mother not being affected by known chronic or systemic diseases, no consumption of anti-depressant, anti-anxiety, or anti-stress medications in their recent pregnancy, no history of asthma, allergy, or dermatitis diagnosed by a physician, no history of eczema and allergy to flowers and plants diagnosed by a physician, and no

disorder in olfactory sense. Exclusion criterion was appearance of signs of allergy to lavender essential in the subjects or their family members. Firstly, the subjects' background characteristics questionnaire was filled. Then, the subjects were randomly assigned to study (aromatherapy) and control (no aromatherapy) groups by picking up the cards of the related groups.

One subject in the aromatherapy group in the first stage of sampling and two subjects in the control group (one in the first stage and the other in the second stage of sampling) were left out of the study as they developed acute anxiety. Also, 27 subjects were excluded in the first stage of sampling as they were not willing to continue in the study. One subject was excluded due to her claim that lavender was unpleasant. Intervention in the study group consisted of inhalation of lavender essential (prepared from the leaves of lavender plant) manufactured by Golkaran company (Kashan, Isfahan). Firstly, The mothers were trained how to inhale the aroma, subsequently administered the process once Under supervision of the researcher. In the study group, the subjects took three drops of lavender essential on their palms, rubbed them together three times a day (with an 8 h interval), and continued the intervention for 4 weeks after discharge from the hospital. The subjects were followed up through phone calls to find out if they did the intervention and had no allergy to the lavender essential. The subjects in both groups filled the Edinburg stress, anxiety, and depression scale and the 21-item Depression, Anxiety, and Stress Scale (DASS-21) questionnaire 2 weeks, 1 month, and 3 months after intervention. During the follow-up period, the women receiving high scores of stress, anxiety, and acute depression were excluded and referred to a psychiatrist. Data collection tools were demographic characteristics questionnaire and a checklist including standard Edinburg test and DASS-21. Edinburg standard test includes 10 four-option questions, each scored between 0 and 3. Based on Edinburg questionnaire, the subjects with scores less than 13 were not depressed and those with scores equal to or higher than

13 were counted as depressed. Edinburg 10-item standard questionnaire was designed by Cocks *et al*. in 1978 and has been frequently adopted for diagnosis of depression. Its sensitivity and specificity and prediction value have been confirmed in Iran. [6] DASS-21 standard scale of depression, anxiety, and stress is a self-reporting 21-item questionnaire that is capable of evaluating depression, anxiety, and stress concurrently. Each of the three subscales of depression, anxiety, and stress contains seven questions. The subjects' score in each subscale is calculated by adding up all subscale scores. In this questionnaire, the items are scored between 0 and 3. DASS-21 has been investigated in some studies; Among them is a study of Honari and Vekraford (2005), which was conducted with a large sample size in England (1794). [21]

In their study, Cronbach alpha values for the scale overall and the three subscales of depression, anxiety, and stress were reported as 0.93%, 0.88%, 0.82%, and 0.90%, respectively.

Factor analysis also confirmed the subscales of depression, anxiety, and stress (each with seven items). Validity and reliability of DASS-21 have been frequently investigated and established. [22] The resultant data of study were analyzed by SPSS19, ANOVA, Mann-Whitney, *t*-test, and post hoc tests. $P < 0.05$ was considered significant.

Go to:

Results

In the present study, 140 women who were hospitalized in the maternity unit were studied after delivery. The background characteristics of both groups have been presented in Table 1 (there was no significant difference in the background characteristics). Variance analysis results showed a significant difference in depression scores between the study and control groups at 2 weeks, 1 month, and 3 months after delivery ($P < 0.0004$). Mean score of depression was

lower in the study group in different time points, compared to the control group ($P < 0.0001$) [Table 2]. Variance analysis results showed a significant difference in the mean scores of anxiety between the study and control groups at 2 weeks, 1 month, and 3 months after delivery ($P < 0.0001$).

Table 1

Background characteristics of subjects in the study and control groups

Descriptive statistics	Test No. (%)	Test No. (%)	Total No.(%)	*P*, *t*
Education				
Under diploma	26 (44.1)	33 (55.9)	59 (100)	*P*=0.599 *t*=1.873
Diploma	32 (55.2)	26 (44.8)	58 (100)	
University education	12 (47.8)	11 (52.2)	23 (100)	
Delivery mode				
Natural	29 (53.7)	25 (46.3)	54 (100)	*P*=0.487 *t*=0.482
Occupation				
Homemaker	67 (50)	67 (50)	134(100)	*P*=10.00
Type of pregnancy				
Unwanted	8 (57.1)	6 (42.9)	14 (100)	*P*=0.573 *t*=0.317
Child's gender				
Unwanted	12 (46.2)	14 (53.8)	26 (100)	*P*=0.664 *t*=0.189
Social satisfaction				
None	4 (36.4)	7 (63.6)	11 (100)	*P*=0.346 *t*=0.888
Marital satisfaction				
None	3 (37.5)	5 (62.5)	8 (100)	*P*=0.466 *t*=0.530
Economic status satisfaction				
None	10 (55.6)	8 (44.4)	18 (100)	*P*=0.614 *t*=0.255

Table 2

Comparison of mean and standard deviation (SD) of stress, anxiety, and depression scores between the two groups in different time points

Time	Group	Stress		Anxiet
		Mean (SD)	*P* value*	Mean (SD)
Two weeks after intervention	Study	5.31 (4.42)	0.012	2.19 (2.42)
	Control	7.34 (5.16)		3.63 (3.88)
One month after intervention	Study	4.10 (3.92)	0.001	1.27 (2.15)
	Control	7.59 (5.14)		4.46 (3.66)
Three months after intervention	Study	3.81 (3.48)	0.001	1.23 (1.94)
	Control	7.27 (5.11)		4.13 (3.43)
ANOVA significance level to investigate the effect of time		0.001		0.001
ANOVA significance level to investigate the effect of group		0.001		0.001

*Mann-Whitney test. SD: Standard deviation

Mean scores of anxiety were lower in the study group in different time points, compared to the control group ($P < 0.0001$) [Table 2]. Variance analysis results showed a significant difference in the mean scores of stress between the study and control groups at 2 weeks, 1 month, and 3 months after delivery ($P < 0.0001$). It was less in the study group compared to control group ($P < 0.0001$) [Table 2]. As observed in Table 3, Chi-square test showed a significant difference in the level of depression in the two groups of study and control at 2 weeks ($P = 0.023$), 1 month ($P < 0.0001$), and 3 months ($P < 0.0001$) after delivery.

Table 3

Comparison of frequency distribution of depression between the two groups in different time points

Time	Group	No. (%)		*P* value*
		Study	Control	
Two weeks after intervention	Depressed	13 (18.6)	25 (35.7)	0.023
One month after intervention	Depressed	2 (2.9)	21 (30.0)	0.001
Three months after intervention	Depressed	3 (4.3)	17 (24.3)	0.001

*Chi-square

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DISCUSSION

This study was conducted to investigate the effect of lavender on the prevention of stress, anxiety, and postpartum depression in women. The obtained results showed that mean differences of stress, anxiety, and postpartum depression scores and incidences of their signs were significantly lower at the time point of 2 weeks after delivery in the study group compared to the control group. Mean differences in the scores of stress, anxiety, and depression at time points of 1 month and 3 months after delivery were significantly different in the study and control groups; therefore, aromatherapy with lavender had a positive effect on reducing their signs. Mean scores of stress, anxiety, and postpartum depression had a higher reduction in the study group compared to control at 2 months after the intervention, indicating the longevity of lavender aromatherapy effect. Mean differences in the scores of stress, anxiety, and postpartum depression were significantly different at 2 weeks, 1 month, and 3 months after delivery between the study and control groups. Meanwhile, mean differences in the scores of stress, anxiety, and postpartum depression were different between the study and control groups at time points of 2 weeks, 1 month, and 3 months after delivery. So, the mean scores of stress and postpartum depression decreased through time in women after delivery. Therefore, although they normally decrease through time, this decrease was higher with lavender aromatherapy, which

prevents or reduces the complications resulting from stress, anxiety, and postpartum depression.

Our results are in line with Sahebalzamin *et al*., who reported a significant reduction of anxiety and depression of the students residing in a hostel after lavender and rose essential aromatherapy, [9] and Mirzaei *et al*., who reported a significant reduction in cortisol release from the adrenal gland, an increase in serotonin secretion from the digestive system, and reduction of anxiety level during delivery after aromatherapy with lavender. [16] Our obtained results are also consistent with the study results of Imura *et al*. on the application of aromatherapy after delivery, reporting an improvement in mothers' and infants' physical and psychological conditions as well as facilitation of maternal-infant interaction, [18] and Conrad and Adams on the effect of inhalation and hand aromatherapies with a combination of lavender and rose essentials, in which hand massage aromatherapy was more effective. [15] It should be noted that in all conducted researches, the goal was reduction of stress, anxiety, and diagnosed depression, while the present study was conducted to prevent these disorders and also investigate the longevity of aromatherapy, which had been ignored in previous studies. The present study faced limitations such as studying the subjects immediately after delivery. Especially those who have underwent CS, were reluctant to fill the psychological status questionnaire due to unappropriate physical and psychological conditions. The questionnaires were not also completed before intervention. In order to overcome this limitation and having two identical groups with regard to psychological conditions.

- Conducting random sampling, meeting the inclusion criteria, investigating any diagnosed incidence or history of mood and psychological disorders before entering the study
- Although the subjects were randomly selected and aromatherapy was conducted in two phases of "at home" and "in hospital," where the

study and control subjects could be hospitalized on the beds next to each other and could distinguish the difference between lavender essential from placebo making a bias in the study, no intervention except routine care was administered in the control group.

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Conclusion

As inhalation of lavender can lead to prevention of stress, anxiety, and postpartum depression, it can be used as a complementary method to prevent these disorders.

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Conflicts of interest

There are no conflicts of interest

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