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Review

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

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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

Abbreviations: BAI, Beck Anxiety Inventory; CBT, cognitive-behavioral therapy; DASS, Depression Anxiety Stress Scale; DBP, Diastolic Blood Pressure; EMA, European Medicines Agency; FAS, Face Anxiety Scale (FAS); GABA, gamma-aminobutyric acid; GAD, Generalized Anxiety Disorder; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HMPC, Herbal Medicinal Products; HR, Heart Rate; HRV, Heart Rate Variability; MDAS, Modified Dental Anxiety Scale; NRSs, Non-Randomized Studies; POMS, Profile of Moods Scale; RCTs, Randomized Controlled Trials; RR, Respiratory Rate; SBP, Systolic Blood Pressure; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; STAI, Spielberger's State and Trait Anxiety Inventory; VAS, Visual Analog Scale (VAS); Zung-SAS, Zung Self-reported Anxiety Scale

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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

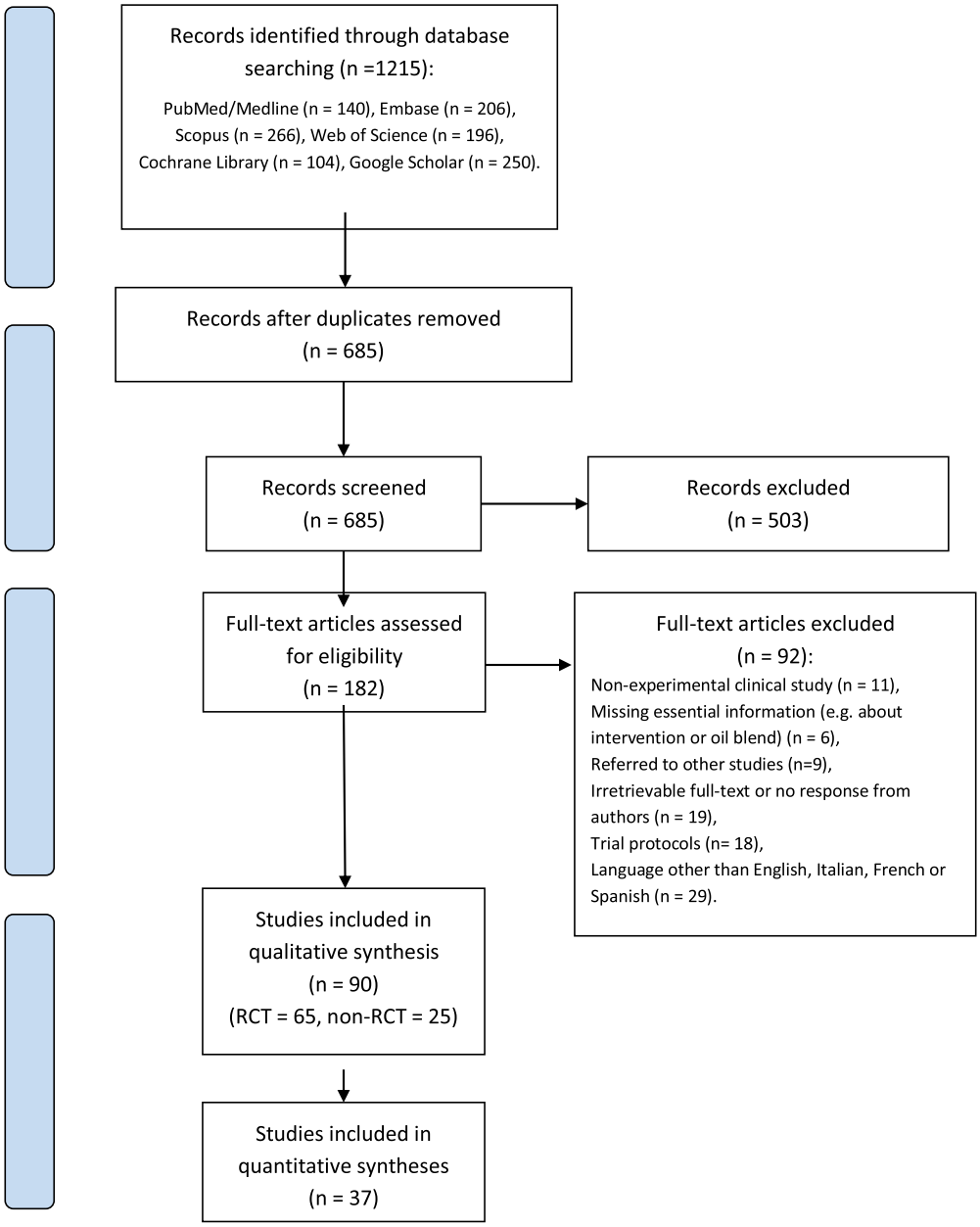

Fig. 1. PRISMA flow diagram of the systematic review and meta-analysis (adapted from Liberati et al., 2009).

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]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
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	(40) Standard nursing preoperative care		STAI	Y	N	Y	Y	H	H
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	(34) No intervention (only observation)	(34) Isometric exercise	STAI	Y	N	N	Y	H	H
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	(34) No intervention (only observation)	(34) Reflexology	STAI	Y	N	N	Y	H	H
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	(37) Usual care		HADS	N	N	N	N	H	H
Bahrami et al.-(2017)	(90) Patients with Acute Coronary Syndrome	Elderly	Not specified	Lavender oil diluted in almond oil. Massage for some minutes.	45	(45) Usual care		HADS, SBP	NR	NR	Y	Y	U	H
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	(50) Lemon juice 0.1% frictioned under the nose and inhaled for 60 s		STAI-S, VAS	Y	N	NR	Y	H	H

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Bekhradi and Vakilian-(2016)	(112) Female university students with test anxiety	Adults	*Lavandula angustifolia* Mill	10% lavender oil. Inhalation overnight, once a week.	61	(42) No intervention		Test anxiety scale	NR	NR	N	N	H	H
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	(30) Inhalation of distilled water		DASS-21, SBP, DBP, HR, HF	Y	Y	N (Y for SBP)	N	l	l
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	(49) Usual care	(50) Sham (usual care as control group plus jojoba oil). Inhalation.	VAS anxiety scale	Y	NR	N	Y	l	H
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	(31) Placebo capsules	(32) 100ul lavender oil containing capsules	STAI-S	Y	N	Y	Y	H	H
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	(25) Water inhalation (placebo)	(26) Rosemary oil (5 drops diluted in 30 ml distilled water). Inhalation of 3 drops for 10 min	POMS, Temperature; HR	NR	NR	Y	Y	H	H
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	(30) Peppermint essential oil	(35) No intervention	STAI-S	NR	NR	Y	Y	H	H

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Diegoetal.(1998)	(40) Medical school staff members	Adults	Not specified	Lavender essential oil 10% in grapeseed oil, 3 drops on a cotton swab placed under the nose for 3 min.	20	(20) Rosemary essential oil 10% in grapeseed oil, 3 drops on a cotton swab placed under the nose for 3 min.		STAI-S, POMS, EEG	Y	Y	NR	U	H	H
Dunnetal.(1995)	(93) Intensive-care unit patients	Adults/ Elderly	*Lavandula vera*	Aromatherapy massage for 15 min: lavender essential oil diluted to 1% concentration.	21	(23) 17 min of massage (with grapeseed oil)	(22) Undisturbed rest, for 35 min	SBP, HR, RR, 4-point scale tool for anxiety	Y	Y (undisturbed rest group)	N	Y	H	H
Effati-Daryanietal.-(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)	Lavender + footbath: 46; Lavender cream only: 47	(44) Placebo cream		DASS-21	NR	NR	Y	Y	U	H
Farshbaf-khalili et al.(2018)	(156) Postmenopausal women	Adults	Not specified	Lavender dried flowers, powder capsules (500 mg per capsule). Oral administration, twice a day for 8 weeks	52	(51) Bitter orange capsules	(52) Placebo capsules	STAI	NR	NR	Y	Y	U	U
Franco et al.-(2016)	(93) Women undergoing breast surgery	Adults	*Lavandula angustifolia*	Lavender oil, 2 drops (2% concentration). Inhalation: 10 min	43	(45) Inhalation of 2 drops of unscented oil		SBP, HR, STAI-S	Y	Y	Y	Y	U	H
		Adults			13			STAI-S	NR	NR	N	N	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
Gnatta et al.-(2011)	(35) First year nursing university students		*Lavandula officinalis*	Lavender oil diluted in a gel base (0.5% lavender oil). Massage 3 times a day for 60 days		(10) Geranium essential oil gel	(12) Rose essence gel							
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 reported	(Not reported) Carrier oil only	(Not reported) Carrier oil with fractionated low grade essential oils	HADS, SPHERE subscale GHQ	NR	NR	N	N	H	H
Grunebaum et al.-(2011)	(30) Patients undergoing Botox injections for the first time	Children/ Adolescents	Not specified	Lavender oil diluted in water (3 drops in 60 ml water). Inhalation	Not reported	(Not reported) Placebo (inhalation of water)		STAI, HR	N	N	N	U	H	H
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	(35) Sham inhalation (10 drops of sesame oil)		SBP, DBP, RR, HR	Y	Y (SBP)	Y	Y	l	U
Hosseini et al.-(2016)	(90) Subjects undergoing open heart surgery	Adults	Not specified	Lavender essential oil (2 drops), inhalation for 20 min	45	(45) Inhalation of 2 drops of sterile water		STAI, Cortisol levels	Y	NR	Y	Y	U	H
Howard and Hughes-(2008)	(96) Young healthy undergraduates	Adults	Not specified	Lavender essential oil, inhalation	32	(30) No intervention	(30) Placebo-aroma	STAI, GSR	N	NR	Y	N	H	H
Hoya et al. (2008)					26				N	N	NR	Y	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	(50) Patients undergoing gastroscopy	Adults/ Elderly	Not specified	Lavender oil aromatherapy 15 min prior to gastroscopy		(24) Usual care		Face Scale Score, SBP						
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	(73) Usual care	(73) Placebo (vapor without essential oil).(71) Grapefruit oil, aromatherapy (74) Osmanthus oil, aromatherapy	Numeric Rating Scale for anxiety	N	NR	N	N (for lavender)	l	U
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	(7) Usual care		STAI, VAS, HRV, HR	Y	N	Y	Y	H	H
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	(6) Resting in seated position for 5 min		POMS, HR, HRV	Y	N	N	U	H	H
Karadag et al.-(2017)	(60) ICU coronary patients	Adults	Not specified	Lavender oil (2%, 2 drops diluted in water) Inhalation every night for 15 days	30	(30) Usual care		BAI	Y	N	Y	Y	H	H
		Adults			51				Y	N	Y	Y	l	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
Karaman et al.-(2016)	(106) Peripheral Venous Cannulation in patients undergoing surgery		*Lavandula angustifolia*	Lavender oil (2%), 2 drops. Inhalation for 5 min before cannulation		(50) Placebo		VAS-anxiety scale						
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	(90) Placebo capsules		HAMA, SAS	NR	NR	Y	Y	l	l
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	Silexan 160 mg: 103; Silexan 80 mg: 119	(114) Paroxetine capsules (identical to Silexan ones)	(114) Placebo capsules	HAMA, CAS, HAMD	NR	NR	Y	Y	U	U
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	(84) Placebo capsules		HAMA, SAS	NR	NR	Y	Y	H	H
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	(156) Placebo capsules		HAMA	NR	NR	Y	Y	H	H
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	Silexan 80 mg: 103; Silexan 40 mg: 100; SIlexan 10 mg: 97	(102) Placebo capsules		HAMA	NR	NR	N	U	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
Kavurmaci et al.-(2015)	(154) Nursing students	Adults	Not specified	Lavender oil (3 drops on cloth). Inhalation for 15 min before, and during the examination.	42	(49) No intervention		STAI	NR	NR	Y	Y	U	H
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	(35) Usual care		STAI	Y	N	Y	Y	H	H
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	(70) Usual care		DASS-21	Y	N	Y	Y	H	H
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	(170) Placebo (candle warmer without essential oil)		MDAS, STAI-6	NR	NR	Y	Y	H	H
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	(45) No intervention		STAI	NR	NR	Y	Y	H	H
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	(30) Back massage with only almond oil		STAI	NR	NR	Y	Y	H	H
Lee et al. (2017)					52				NR	NR	Y	Y	l	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	(132) ICU patients undergoing mechanical ventilation	Not reported	Not specified	Lavender oil (2%). Aromatherapy massage for 20 min, then resting for 20 min		(56) Music group, 30 min listening session	(52) Control group (only rest for 30 min)	VAS 100 mm scale, C-STAI, RR, SBP, DBP, MAP, HR						
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 reported	(Not reported) Inhalation of water on a cotton pad, diffusion		HR, HF power, POMS	NR	NR	N	Y	H	H
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	(9) Yuzu oil (diffusion)		HR, HF power, POMS	Y	Y	N	Y	H	H
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	(30) Inhalation of sterile water		STAI, SBP, DBP	Y	Y	Y	Y	H	H
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	(57) Control grapeseed oil 3 drops on a cotton ball, inhaled for 5 min at 4in of distance from the nose		STAI-S	N	N	NR	N	H	H
Najafietal.(2014)	(70)	Adults/ Elderly	*Lavandula stoechas*	Lavender oil (3 drops).	33	(35) Usual care		STAI	Y	N	Y	Y	U	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	Myocardial infarction patients			Inhalation (20 min) twice a day for the second and third day of hospitalization										
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	(50) Usual care		VAS	NR	NR	Y	Y	H	H
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	(30) Usual care		STAI	Y	N	Y	Y	H	H
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	(20) Tea tree oil (3 drops on a piece of cotton) inhalation	(20) Usual care	STAI	Y	N	Y	Y	l	H
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	(30) Usual care		RR, HR, SBP, DBP, DASS	NR	NR	Y	Y	H	H
Sanei and Chasmi-(2018)	(45) First year high	Children/ Adolescents	*Lavandula angustifolia*	Fresh extract of lavender, to drink (10 ml of	Group2: 15;	(15) No intervention		TAI	Y	NR	Y	Y	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	school students			extract mixed in a glass of water). Each night for the period preceding exams (20 days for 2nd group, 3 days for 3rd group)	group3: 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	(30) Placebo, 2 drops of distilled water on a patch inside an oxygen mask		STAI, SBP, DBP, HR, RR, Temperature	Y	Y	Y	N	H	H
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	(17) Usual care		PSQI, HAMA	Y	N	Y	Y	H	H
Seyyedrasooli 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)	Lavender inhalation group: 30. Lavender massage group: 30.	(30) Usual care		STAI	Y	N	Y	Y	U	H
Sgoutas-Emch et al.- (2001)	(80) Undergraduate	Adults	Not specified	Lavender oil, diffusion	Group1: 17;	(15) Group 2: Placebo	(12) Group 4: patients	SIMA, STAI, APQ anxiety,	Y	Y	N	N	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	university students in stressful situation			aromatherapy.Group 1: patients being told they would receive aromatherapy and received the therapy while doing the task; Group 3: patients being not told anything about aromatherapy but received the treatment	group3: 18	effect (patients being told they were receiving aromatherapy but actually received nothing)	being not told anything about aromatherapy, did not receive it	HR, SBP, DBP						
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	(53) Placebo (diluted milk from a bottle identical to intervention group)		STAI, SBP, DBP, HR	Y	N	Y	Y	l	l
Sodenetal.(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	(13) Placebo (massage with only sweet almond oil)	(13) Usual care	HADS	N	Y (massage)	N	N	H	H
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	(30) Placebo (peppermint-orange blend aromatherapy tabs)	(27) Placebo (no-scent tabs looking identical to other aromatherapy tabs)	SBP, DBP, HR, RR, STAI	Y	Y	Y	Y	H	H
Tugutetal.(2017)	(156) Women undergoing	Adults	Not specified	10% lavender essential oil on a lamp diffuser, 15 cm from the table during	78	(78) Usual care		STAI-S	Y	N	Y	Y	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	gynecological examination			gynecological examination (15 min)										
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 end it when the cycle started	40	(37) No intervention		PMS scale: anxiety subgroup	NR	NR	Y	Y	H	H
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	(50) Placebo (odourless candle warmer with only water)		MDAS	NR	NR	Y	Y	H	H
Woelk and Schläfke-(2010)	(77) GAD (generalized anxiety disorder) patients	Adults	*Lavandula angustifolia* (Silexan)	Silexan capsules (80 mg), oral administration, for 6 weeks	36	(33) Lorazepam tabs/ placebo tabs in no intervention days		HAMA, SAS	Y	NR	Y	Y	H	H
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	(16) (all patients received both shirodara treatments and placebo). Shirodara with plain sesame oil	(16) Placebo shirodara (control study).	STAI, Skin Temperature, HRV	Y	Y (sesame oil group)	N	Y	H	H
Zabirunnisaetal.-(2014)	(597) Patients awaiting dental	Adults	*Lavandula angustifolia*	Lavender oil diluted in water (ratio 1:1) in candle warmers	287	(310) Candle warmers		MDAS	NR	NR	Y	Y	H	H

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Table 1 (*continued*)

Author (Year)	(No. of randomized patients) Population characteristics[a]	Age[b]	Lavender species	Intervention type[c]	Intervention Group (n)[d]	(No. of patients) Type of control group 1[e]	(No. of patients) Type of control group 2[f]	Anxiety outcome[g]	Significant anxiety improvement *within intervention* group[h]	Significant improvement *within control* group[i]	Significant difference *between* groups *after* intervention[j]	Authors' conclusions[k]	Overall risk of bias (PB as a non-key domain)[l]	Overall risk of bias
	procedures in dental office			placed in the waiting room. Aroma diffusion: 15 min exposition while in the waiting room		with only water								
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	(40) Cotton wool soaked with distilled water		STAI	Y	N	Y	Y	U	H

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.

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.

Information sources

Medline via PubMed, Scopus, Web of Science, Cochrane Library, EMBASE, and Google Scholar were systematically searched for relevant articles.

All mentioned databases were screened up to November 2018.

Search

The following search strategies were used:

- PubMed/Medline: "((Lavender[Title/Abstract] OR lavandula[Title/Abstract] OR silexan[Title/Abstract])) AND (anxiety[Title/Abstract] OR anxious[Title/Abstract] OR anxiolytic[Title/Abstract])".
- Scopus: "(TITLE-ABS-KEY (lavender OR lavandula OR silexan) AND TITLE-ABS-KEY (anxiety OR anxious OR anxiolytic)) ".
- Web of Science: "TOPIC: (lavender OR lavandula OR silexan) AND TOPIC:(anxiety OR anxious OR anxiolytic)".
- Cochrane library: lavender OR lavandula OR silexan AND anxiety OR anxious OR anxiolytic in Title, Abstract, Keywords.
- EMBASE: "('lavender':ab,ti OR 'lavandula':ab,ti OR 'silexan':ab,ti) AND ('anxiety':ab,ti OR 'anxious':ab,ti OR 'anxiolytic':ab,ti)"
- Scholar: "(lavender OR lavandula OR silexan) AND (anxiety OR anxious OR anxiolytic)"

Study selection

Details about selection process of studies eligible for this review were summarized in a flowchart (Fig. 1). Results were screened and selected by two investigators independently (M.A., C.B.). In case of disagreement, items were evaluated by a third author (D.D.) and then discussed until consensus was reached. The above mentioned PICOS criteria for inclusion and exclusion of studies in the systematic review were thoroughly applied.

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".

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.

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.

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.

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.

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).

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.

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.

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, $50\% < I^2 < 75\%$

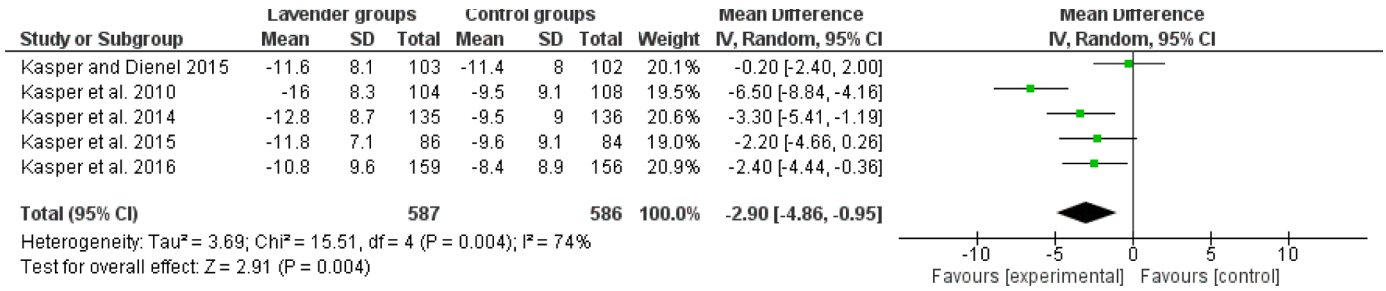

Fig. 2. Forest plot referred to the meta-analysis about effects of Silexan® at a dose of 80 mg/die on anxiety levels (pre-post intervention changes in HAMA total score) compared to placebo. Description: Anxiety levels (measured with HAM-A questionnaire) mean changes-from-baseline after intervention (Silexan®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

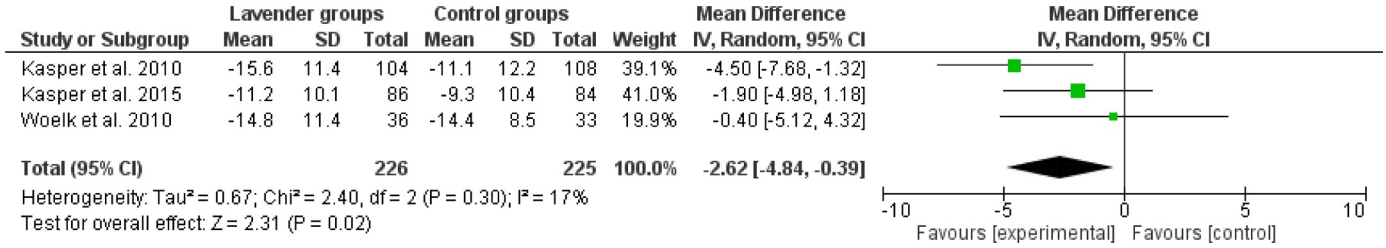

Fig. 3. Forest plot referred to the meta-analysis about the effects of oral administration of Silexan® at a dose of 80 mg/die on anxiety levels (pre-post intervention changes in Zung SAS score) compared to placebo. Description: Anxiety levels (measured with Zung SAS score) mean changes-from-baseline 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.

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

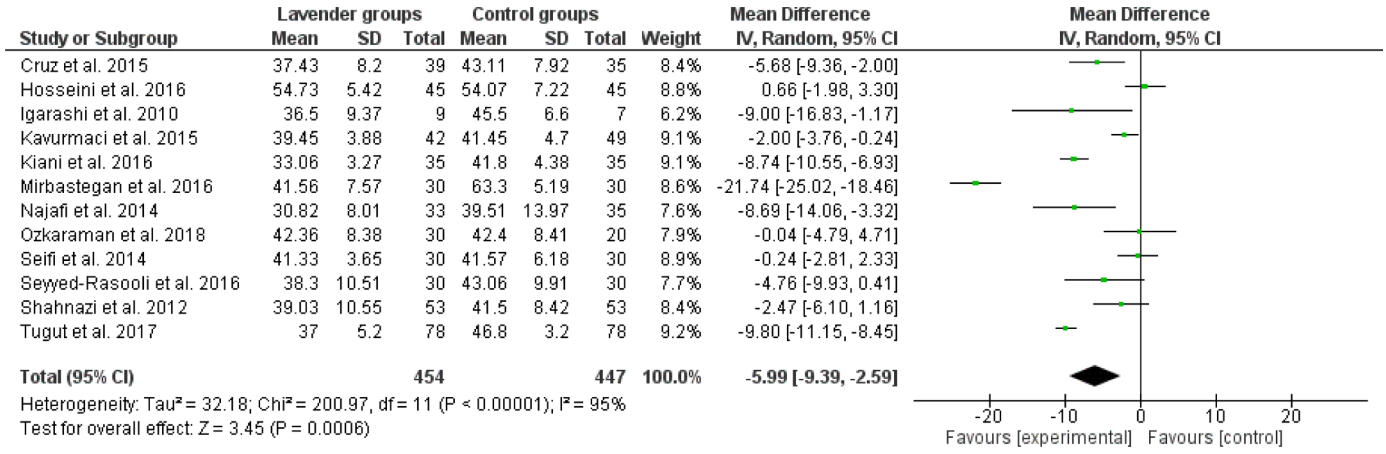

Fig. 4. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on anxiety levels (STAI-S score after intervention) compared to no intervention or usual care. Description: Anxiety levels (measured with STAI-S questionnaire) after intervention (lavender essential 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.

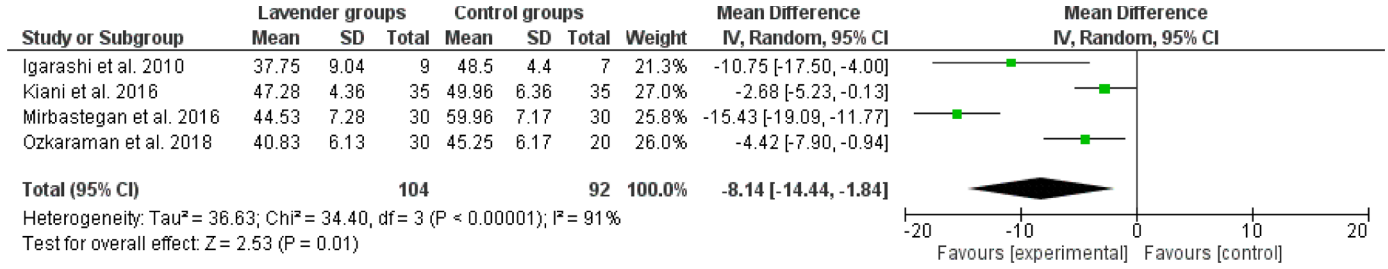

Fig. 5. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on anxiety levels (STAI-T score after intervention) compared to no intervention or usual care. Description: Anxiety levels (measured with STAI-T questionnaire) after intervention (lavender essential 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.

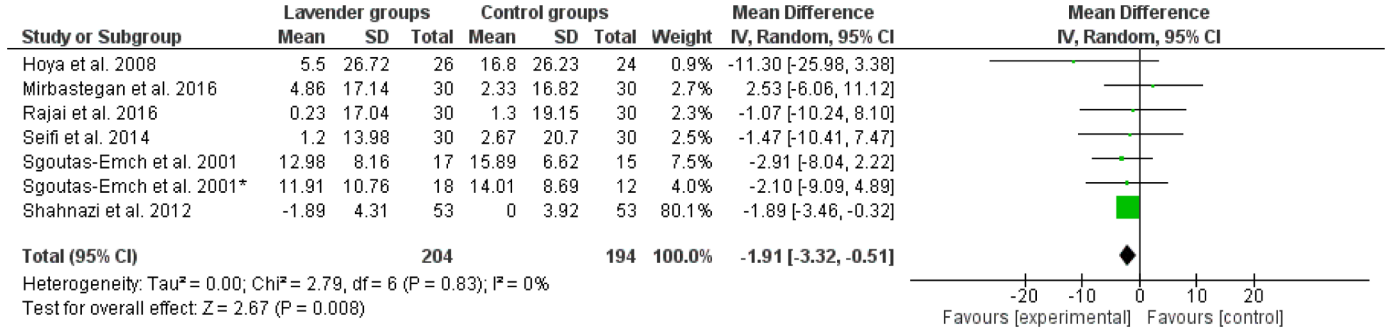

Fig. 6. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on systolic blood pressure (mean changes-from-baseline) compared to no intervention or sham intervention (distilled water or oil without lavender). Description: systolic blood pressure (measured 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.

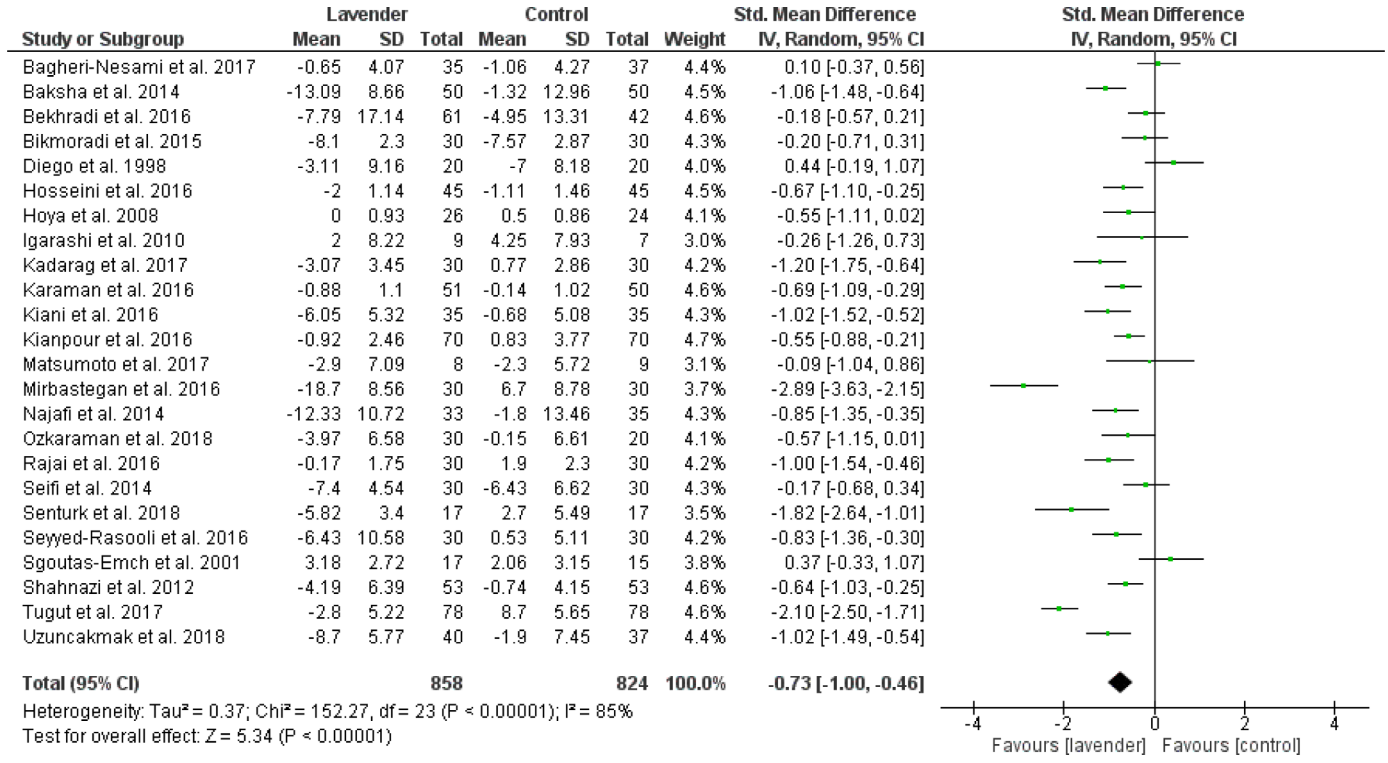

Fig. 7. Forest plot referred to the meta-analysis about the effects of inhalation of lavender essential oil on anxiety levels (pre-post intervention variations assessed with any validated scale) regardless of comparison type. Description: Anxiety levels (measured with any validated scale) mean changes-from-baseline 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.

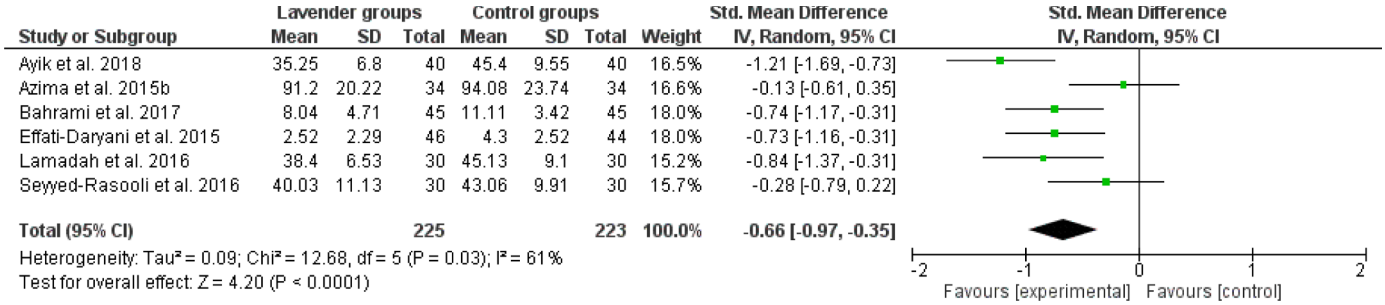

Fig. 8. Forest plot referred to the meta-analysis about the effects of massage with lavender oil on anxiety levels (measured with any validated scale) compared to other physical therapies (reflexology or massage without oil) or usual care. Description: Anxiety levels (measured with any validated scale) 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.

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).

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

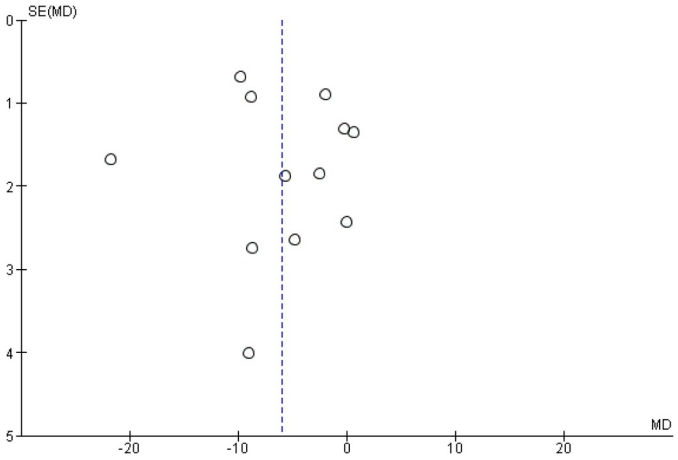

Fig. 9. Funnel plot referred to the third meta-analysis (Inhalation, STAI-S) (Fig. 4).

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).

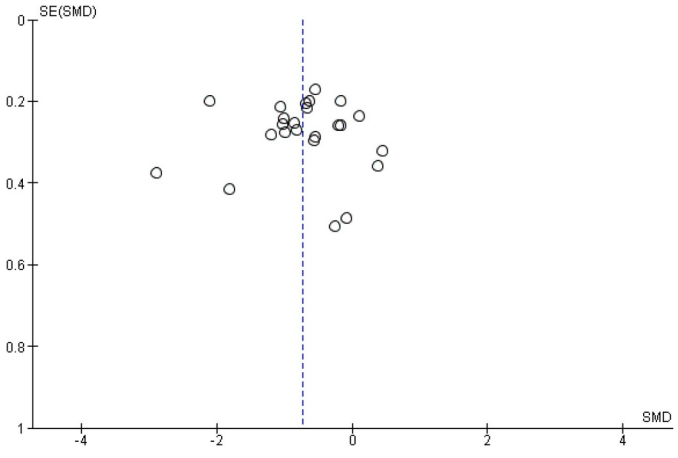

Fig. 10. Funnel plot referred to the sixth meta-analysis (Inhalation, any validated anxiety questionnaire, any comparison type) (Fig. 7).

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2019.153099.

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