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Benefit of inhalation aromatherapy as a complementary treatment for stress and anxiety in a clinical setting – A systematic review

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ABSTRACT

Objective: The purpose of this systematic review is to ascertain the impact of inhalation aromatherapy on stress and anxiety in clinical settings.
Methods: A search strategy was developed using various databases. Randomised Controlled Trials (RCTs) as well as single and double-blind pilot clinical studies (non-RCT) using inhalation aromatherapy with an essential oil blend or a single essential oil were examined. All studies included a control intervention and use of a validated measurement tool. The time period under review was years 2000–2021. Due to the high level of heterogeneity and element of bias, a narrative synthesis was conducted.
Results: The search strategy initially retrieved 628 studies and through application of the selection criteria and the removal of duplicates, 76 studies were selected for review with a total of 6539 patients. In 42% of the RCTs, physiological measures including vital signs and/or salivary cortisol were used in addition to questionnaires. Over 70% of the studies reported a positive effect on anxiety levels in the aromatherapy intervention groups compared with the control. However, in many cases this is limited by the absence of safety data, imprecise reporting of plant species and dosage of essential oil.
Conclusion: Inhalation aromatherapy has the potential to reduce stress and anxiety with data emerging to further support this result across a wide modality of clinical treatments. However, there is a clear need for the development of standard protocols for research in this area, generating measurable results which will create the opportunity for more rigorous evidence-based outcomes.

1. Introduction & background

Aromatherapy is a complementary practice which is defined as the therapeutic use of essential oils extracted from plants to support physical, emotional, and spiritual wellbeing.

Essential oils are volatile liquid substances extracted from plant material by steam distillation or expression. They are mostly extracted from all parts of the plant including flowers, leaves, seeds, resins, roots or bark. These highly concentrated oils are used for inhalation and topical treatments through skin absorption: inhalation treatments are provided using oil infused cloths, nasal sticks or patches, or via room diffusion; when used topically, the essential oils are diluted in a fixed oil at a low concentration and used for touch therapy. Dilution is required due to the potential for skin sensitisation, contact dermatitis and phototoxicity from citrus oils [1,2].

In the commercial marketplace aromatherapy products containing essential oils are sold in pharmacies, health food shops, specialty stores, supermarkets and on the internet. Essential oils are also used widely in cosmetics, room diffusers and in the flavouring and fragrance industry which are governed by cosmetic and consumer product legislation. Consumer demand for essential oils has grown exponentially in recent years due to the interest in natural products to promote health and wellbeing [3].

Early references of plant oils go back to 2000 BCE in Ancient Egypt where resins such as frankincense myrrh and benzoin were used for perfumery, ceremonial sacrifice and ritual. Aromatic plants and plant oils have been part of plant medicine and used since ancient times in the treatment of ailments and disease. The foundations of modern medicine began with Greek physicians Hippocrates (400 BCE) and later by Galen (150–200 AD) [4,5]. The concept of holistic medicine is attributed to Hippocrates who considered the "whole" person from a medicinal point of view - mental, emotional and physical. In this regard, aromatherapy is

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considered a "holistic therapy", a concept which it shares with other practices such as Traditional Chinese Medicine (TCM) and Ayurvedic medicine [6,7].

The French chemist, Rene-Maurice Gattefossé (1881–1951) is considered the father of modern aromatherapy. He developed the practice of aromatherapy in the 1920s and coined the term "*aromatherapie*". Gattefossé considered aromatherapy to be fundamentally based in medicine with an emphasis on the chemistry of the essential oils and their active constituents. Gattefossé was the first to consider the synergy of essential oils when combined in a blend, a concept which forms the basis of contemporary aromatherapy practice [6,7]. While the principle mode of application of the plant oils was by topical treatment through skin absorption, as a perfumer, Gattefossé also considered the psychological benefit derived from inhaling a natural fragrance and its olfactory response [8].

Clinical studies have examined the role of the olfactory response following inhalation of essential oils. Once inhaled, the volatile molecules trigger a nerve impulse in the olfactory pathway entering the limbic system in the brain where they are processed in the amygdala and hippocampus [9]. The amygdala elicits an emotional response and the hippocampus is responsible for the associated memory and learning linked to a past event or experience. Studies have shown that odour induced memories and positive associations can have a positive impact on mood, health and wellbeing [9,10]. Inhalation aromatherapy may also react with the automatic nervous system to aid relaxation and reduce stress levels [11–13].

Traditionally, an aromatherapy treatment is based on a one-to-one therapist-patient relationship that typically involves: a consultation of medical and lifestyle history, preparation of a customised blend of plant oils specifically for the client about the therapeutic properties of the oils, cultural practice, anecdotal and scientific evidence, safety and dosage. The treatment can be given via massage or with a personal blend of oils provided for inhalation purposes. The aroma and the role of olfaction and its potential psychological benefits form an integral part of the treatment [14]. In *Hemodyialysis International,* Lee et al. reported that the aromatherapy intervention provided "immeasurable comfort to dialysis patients" [15].

In the last 30 years, aromatherapy has developed as a clinical practice providing complementary therapy in clinical settings through massage and inhalation and has been the subject of a growing number of clinical studies investigating its potential as a non-pharmacological intervention [16–18]. While healthcare professionals are primarily concerned with resolving illness, they are becoming increasingly aware of the need to provide a patient-centred approach to support patient's psychological wellbeing [18–20]. There is growing evidence that the aromatic compounds in an essential oil can have sedative and anxiolytic effects [21]. Studies have shown that specific essential oils can reduce anxiety and offer simple, accessible, low-risk and cost-effective interventions that improve the overall patient outcome [22–24].

In oncology and palliative care, aromatherapy has been used primarily as a beneficial, safe and non-invasive complementary treatment. While conventional cancer treatments have seen a reduction in rates of mortality, patients often suffer from adverse side effects that lead to fatigue, postoperative pain, nausea, insomnia and anxiety that can have a negative impact on their psychological wellbeing and quality of life. Complementary therapy units have been incorporated into cancer hospitals and hospices and are offered as a service to patients during their treatment [10,14,25]. The use of aromatherapy as a patient support has been embraced by obstetrics, pain management, dentistry and procedural anxiety [26–29]. However, the lack of an appropriate control groups and a strong element of bias in many studies has limited the findings. There is need for more robust evidence which will be discussed further.

2. Materials & methods

This review has been registered at the PROSPERO database (ID: CRD42022360482).

2.1. Search strategy & selection of articles

The electronic databases in the search selection included Embase, PubMed/Medline, Cochrane, and Web of Science.

The following concepts and keywords were used when searching the databases:

Concepts: Inhalation aromatherapy, stress and anxiety, clinical settings.

Keywords:

Inhalation aromatherapy: Clinical aromatherapy, essential oil, complementary therapy, room diffusion.

Stress and anxiety: Stress and anxiety, mood, dental anxiety, preoperative anxiety.

Clinical Settings: cancer treatment, surgery, dental practice.

A comprehensive literature search was carried out in scientific databases of peer-reviewed literature from the year 2000–2021 as detailed below.

The PICO Model was used to determine the inclusion and exclusion criteria:

P - Population:

Patients in a stress and anxiety inducing setting or undergoing a treatment.

or procedure that can potentially cause anxiety.

I - Intervention:

Inhalation of single oil or a blend of oils using a nasal spray/ aromastick,

oil infused cotton/patches or room diffusion.

C - Comparison:

Test product and control with a faint aroma, an odourless substance or standard care only.

O – Outcome:

Primary outcome: Evaluate the change in level of stress and anxiety as measured by a validated scale.

Quantitative and qualitative measurements – validated questionnaire, vital signs including heart rate variability (HRV), heart rate and tests for changes in salivary cortisol.

2.2. Study selection and eligibility criteria

Based on the PICO model above the present review examined the studies under the following criteria:

Inclusion Criteria.

Inhalation aromatherapy.

Use of an essential oil blend or a single essential oil.

Publication date from the year 2000–2021.

Randomised Clinical Trial (RCT) or feasibility/pilot clinical study.

Included a placebo or other control intervention.

Mode of intervention – inhalation through essential oil infused cotton gauze/nasal inhaler/aromastick, aromatherapy patches or room diffusion.

Validated quantitative or qualitative measurement including validated questionnaires, HRV, heart rate, salivary cortisol.

English language.

Human studies.

The review was restricted to studies in the English language that may have excluded a number of studies conducted in the use of inhalation aromatherapy in the 2000–2021 time period.

Exclusion Criteria.

Massage, touch therapy, other Complementary and Alternative Medicine (CAM) interventions, animal studies, and clinical trials, which are ongoing or not completed.

The Data was sought under the following variables: author, country of origin, year of publication, study design, sample size, essential oil intervention, control, mode of application, patient population, outcome measurements and effect of the inhalation aromatherapy intervention.

The first author independently extracted the data and manual screening of studies. The citations obtained from the study selection were imported to Endnote 20 software to create a database from the extracted data. The selected studies were subsequently imported into the Covidence Database for Systematic Reviews and independently assessed by a second reviewer in line with the review protocol.

3. Results

3.1. Study selection

A total of 628 articles were extracted from Embase (214), PubMed/Medline [30], Cochrane (239), and Web of Science [31] that were in line with eligibility criteria, i.e., years 2000–2021, human studies and publication language is English (Table 1).

Following the removal of duplicates the total number was 377 articles. Additional articles [32], from an earlier search brought the total to 448.

Then, manual screening was conducted to ensure that each study met all inclusion criteria. Following this, study titles, abstracts and full content were reviewed prior to analysis to ensure the relevant inhalation aromatherapy intervention was included. Aromatherapy is frequently included in a broader research study incorporating other CAM modalities and this became apparent when the full content of a study was reviewed and subsequently excluded from the final review. This resulted in a total of 96 studies. An independent review was carried out for these selected studies via Covidence. The independent reviewer checked especially for the following: a higher risk of bias; lack of a control; small sample size and unclear design and methodology. Any issues raised were discussed and resolved, which resulted in the removal of a further twenty studies. This resulted in a final total of 76 studies for final analysis in the current review (see Fig. 1).

In addition to the 76 studies, eight retrospective patient reviews and evaluation studies that were conducted in clinical settings using aromatherapy as a therapeutic intervention are referred to in the discussion section of this review. While these studies did not include a control, they were considered to be of benefit to the overall context and discussion. Systematic reviews, whilst not within the inclusion criteria, were also included for context and perspective in the discussion section of this review.

3.2. Study characteristics

The 76 studies reviewed involved 6539 participants. Fifty of the clinical studies conducted were randomised controlled trials (RCTs) with 4681 participants. The remaining 26 studies (non-RCTs), were conducted with a total of 1858 participants. The aromatherapy interventions involved inhalation aromatherapy and were conducted in clinical settings with a control used for comparison purposes that consisted of an odourless oil, water, saline, standard care only or no intervention.

Table 1
Database search results.

Concepts	EMBASE	PubMed/ Medline	Cochrane	Web of Science
Inhalation aromatherapy + Stress and Anxiety + Clinical settings	n = 229	n = 143	n = 242	n = 135
FILTERS				
Timeline				
2000–2021	n = 229	n = 136	n = 239	n = 135
Human	n = 229	n = 97	n = 239	n = 78
English	n = 214	n = 97	n = 239	n = 78

The RCTs [33] and the non-RCTs [26] were analysed separately in an Excel document under the following headings: author & year, country, study design, sample size, aromatherapy intervention, control, choice of oil(s), mode of application, outcome measures, author's conclusions and any adverse events reported (See Appendix A and B for breakdown of results).

3.3. Inhalation aromatherapy - randomised controlled trials (RCTs)

The 50 RCTs were conducted across 11 countries. Iran accounted for 58% [29] of the studies, USA 14% [7], Turkey 6% [3], Japan, Taiwan and Korea each with 4% [2] and the remaining Germany, India, UK, Australia and Brazil each conducting one trial (see Fig. 2 below).

The number of clinical trials investigating the use of Inhalation aromatherapy as a non-pharmacological intervention has escalated in the last 5 years (See Fig. 3 below). In the current review, over two thirds of the RCTs (62%) were conducted since 2017 and a total of 94% conducted in the last ten years (since 2012). Based on the criteria, there was no evidence of publication for RCTs using inhalation aromatherapy in the years 2000–2002, 2004–2009 and 2011.

3.3.1. Outcome measurements used in RCTs

Studies examining the potential benefits of complementary therapy have traditionally relied on anecdotal evidence, with few studies using a control or validated measurement tool. Inclusion criteria for this review required that all studies used validated quantitative measurements to examine the impact of the aromatherapy intervention. Combining a validated measure for stress and anxiety with a quantifiable physiological measure strengthened the validity of the study leading to more convincing evidence.

The Spielberger's State-Trait Anxiety Scale (STAI) was the most frequently used measurement tool for stress and anxiety (see breakdown in Table 2 below).

The other validated measurement tools that were used in the studies:

Beck Anxiety Inventory (BAI).
Canter for Epidemiologic Studies Depression Scale (CES-D).
Children's Behavioral Style Scale (CBSS).
Edinburgh Postnatal Depression Scale (EPDS).
Emotionality Activity Sociability and Impulsivity instrument for children (EASI).
Face Image Scale (FIS).
Fatigue Severity Scale (FSS).
Modified Dental Anxiety Scale (MDAS).
Multidimensional Fatigue Inventory (MFI-20.
Numeric Rating Scale (NRS).
Perceived Stress Scale (PSS).
Pittsburgh Sleep Quality Index (PSQI).
Pregnancy Unique Quantization of Emesis (PUQE-24).
Profile of Mood States (POMS).
Quality of Life (QOL).
Richard Sleep Campbell Questionnaire (RCSQ).
The Dental Anxiety Questionnaire (DAQ).

In addition to the anxiety validated scales of measurement, 20 of the RCTs in this review measured vital signs at various time points, before, during and after intervention including heart rate variability (HRV), blood pressure, pulse and respiratory rate. These were measured in studies on the following conditions: procedural anxiety [28,35–44], oncology [45], dental [46–48], stress and sleep [49,50]. Salivary cortisol was measured in five of the studies and four of these reported a reduction in cortisol levels [37,40,50,51] with one reporting no significant change [52].

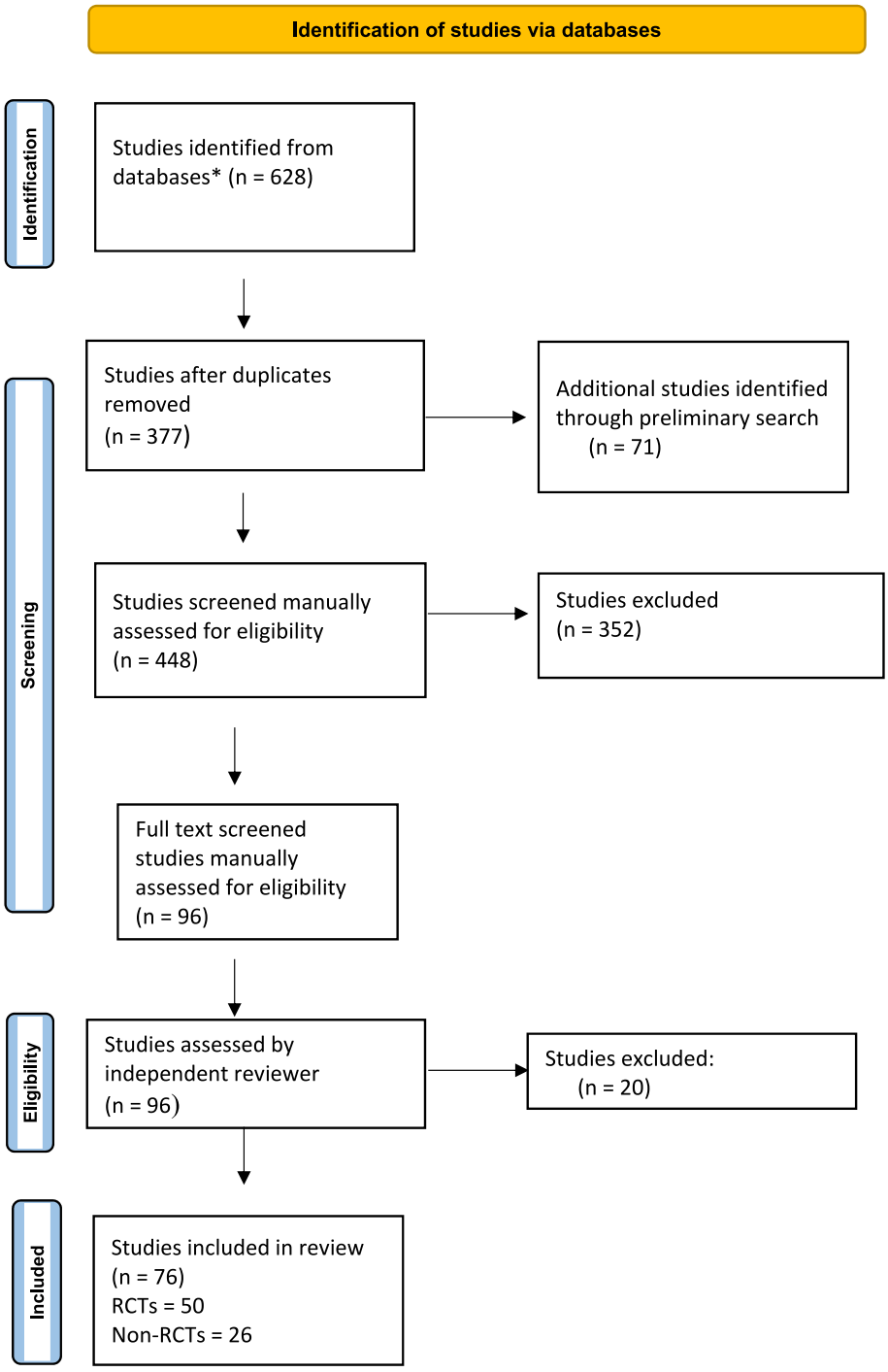

Fig. 1. PRISMA flow diagram of the systematic review data search adapted from Liberati et al. [34]
*See Table 1 for the number of records identified from each database searched.

3.3.2. *Choice of essential oils in RCTs*

Lavender essential oil (*lavandula angustifolia)* is widely recognised for its relaxing and sedative properties and is frequently used in the treatment of stress and anxiety in clinical settings [22,33,53–55]. In this current review lavender accounts for 42% of the clinical trials and in a further 14% of studies, lavender was chosen with another essential oil for comparison purposes in 3- or 4-armed trials [52,56–59]. However, the precise species of lavender was unclear in some studies. Its use was across all modes of application; infused in cotton balls/gauze, oxygen masks, patches, aroma tabs, aromasticks and in room diffusion [37,48, 58,60,61].

Rose essential oil (*Rosa damascena)* (10%) was used in clinical trials conducted in Iran and Turkey. The rose plant is indigenous in both countries and has a long history of use in cultural practice and traditional plant medicine for relaxation. Four of the five studies reviewed reported a reduction in anxiety. The controls were odourless oil, water in ethanol or standard care [62]. The mode of application used in the studies was through room diffusion and in rose oil impregnated in a cotton ball or gauze. In Dehkordi et al. (2017), a group of 60 patients undergoing haemodialysis were enrolled in a study in which the test group was given 3 drops of rose oil (2%) attached to the patient's collar and asked to breathe normally. The control group received standard

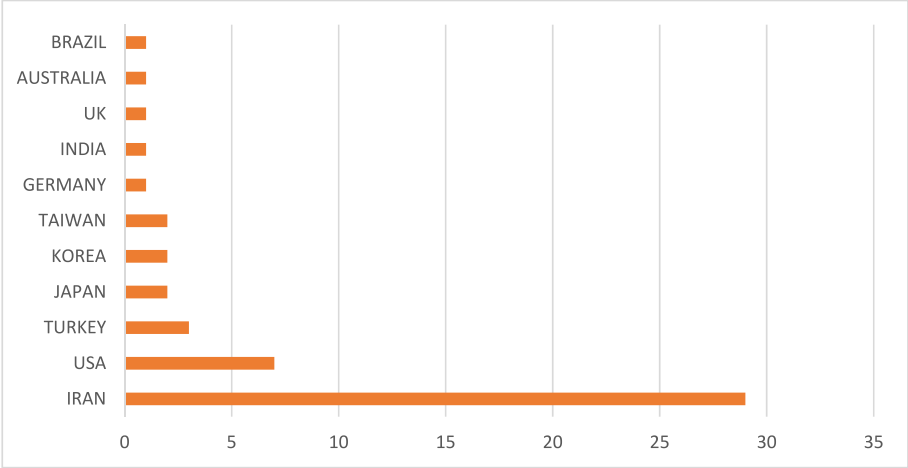

Fig. 2. Number of RCTs using inhalation aromatherapy by country 2000–2021.

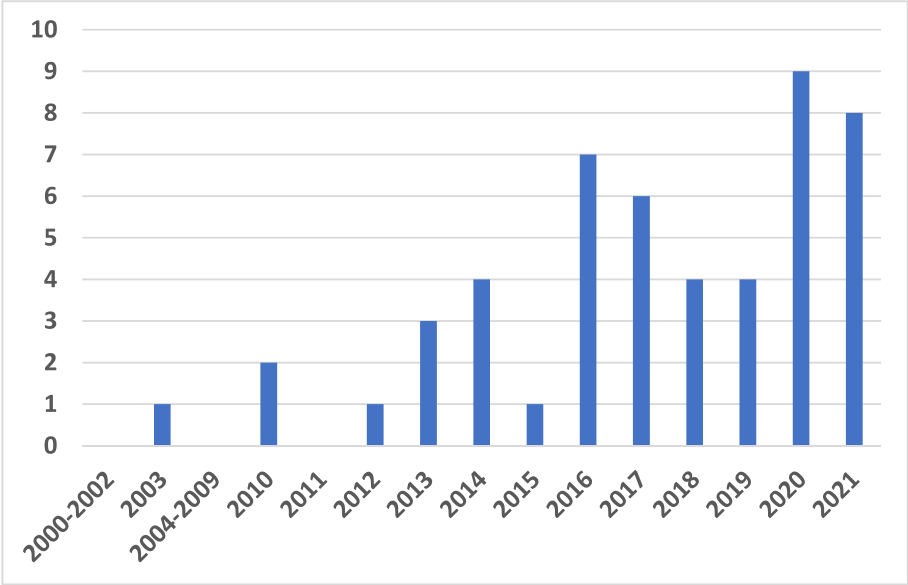

Fig. 3. Number of RCTs using inhalation aromatherapy conducted between 2000–2021.

Table 2
Measurement tools in RCTs.

Measurement Tools used in RCTs	%
Spielberger's State-Trait Anxiety Scale (STAI)	52
Visual Analogue Scale (VAS)	14
Depression, Stress & Anxiety Scale (DASS-21)	12
Hospital Anxiety & Depression Scale (HADS)	8
Others	14

care. Using the Depression, Anxiety and Stress Scale (DASS-21) as a measurement, the test group reported a significant decrease in anxiety scores compared to the control [63].

Next to lavender, rose and orange oils were the most examined essential oils to assess impact on levels of anxiety. In the orange oils, two essential oils come from the bitter orange tree (*Citrus aurantium* x L): neroli oil - orange blossom - (*Citrus* x *aurantium* L/*Citrus aurantium* var. *amara)*; and petitgrain (*Citrus aurantium*) oil extracted from the leaves and twigs of the bitter orange tree. The similarity in botanical names for petitgrain and neroli can be confusing and the specific oil is unclear in the trials unless the common name is included in the methodology as both are often referred to as *Citrus aurantium*. Petitgrain is often compared to lavender and bergamot for its stress relieving properties as it has similarly high levels of linalyl acetate unlike neroli which contains less than 10%. In addition, both have a distinctly different aroma. The sweet orange *(Citrus sinensis)* essential oil come from the sweet orange tree *(Citrus* x *sinensis*) and has a high level of limonene (>90%); These three oils were used in 10% of the studies [38,47,64–66]. Studies in the treatment of dental anxiety have used sweet orange essential oil in adults and children and recent systematic reviews have examined the potential benefits [67–69]. However, while results have been encouraging, they have not been conclusive and in some cases the absence of an appropriate control and the risk of bias, limit the findings [26,47,69]. Bergamot (*Citrus bergamia*) was used in 4% of studies [39,40] for its potential mood boosting properties and stress reduction. The studies reported a positive improvement with the exception of Ndao et al. (2012), which did not determine a change of statistical significance [70].

Blends of essential oils were used in 12% of the studies. In addition to the aforementioned oils, other essential oils were chosen as a single oil intervention, for comparison purposes with another essential oil or used in a blend. These included: roman chamomile (*Anthemis nobilis*), ginger

(*Zingiber officinale*), clary sage (*Salvia scarlea),* lemon *(Citrus limon),* tea tree *(Melaleuca alternifolia),* peppermint *(Mentha x piperita)*, melissa *(Melissa officinalis)*, sweet marjoram *(Origanum majorana),* fennel (*Foeniculum vulgare), osmanthus (Osmanthus fragrans* Lour.*),* hiba wood *(Thujopsis dolabrata*), grapefruit *(Citrus paradisi)* sage *(Salvia officinalis),* cedarwood *(Cedrus atlantica)* and ylang ylang *(Cananga odorata)*. However, in some trials the precise botanical name of the chosen essential oil was unclear which makes analysing the potential therapeutic effect of a specific oil difficult.

3.3.3. Mode of application of aromatherapy intervention in RCTs

For the purpose of this review, one of the inclusion criteria stated that the route of application was via inhalation as opposed to massage or touch therapy. Inhalation of essential oils can be achieved by various methods (see Fig. 5).

(1) Essential oil impregnated cotton ball/gauze

A majority of the RCTs (66%) used drops of essential oil applied onto a cotton ball, piece of gauze or cloth which was then inhaled from by the patient at various timepoints at baseline, during and after the procedure. Depending on the procedure, the essential oil infused item was beside the patient's bed, attached to the collar of the gown or held by the patients to inhale for specified period of the intervention. Over 70% of the studies found that the aromatherapy intervention was positive compared with the control. However, it was difficult to evaluate the studies with any accuracy given the various methods of administration and the absence of the precise quantity of essential oils in many cases.

(2) Aromatherapy patches and tabs

An aromatherapy patch or tab is infused with a single oil or a blend of oils with a self-adhesive tab which can be attached to the skin or gown of the patient for inhalation purposes. They have the advantage over an essential oil infused cotton ball or gauze in that they are consistent in the dose of essential oil absorbed onto the patch/tab and have a sustained release of the constituents overtime. One commercial brand marketed in the USA, *Elequil®,* has been used in US-based clinical trials and has been shown to have a beneficial effect on patient anxiety undergoing procedures for breast biopsy and spinal surgery [71,72]. In *Worldviews on Evidence-Based Nursing*, Trambert et al. (2017) conducted a trial with a group of 87 female patients who were undergoing breast biopsy. Two test *Elequil®* aromatab formulations were used. One was infused with a blend of lavender and sandalwood, the second with orange and peppermint. A third group, which was the control, received a placebo aromatab only. There was a significant reduction in anxiety in the lavender and sandalwood group compared to the other test group and the control [72].

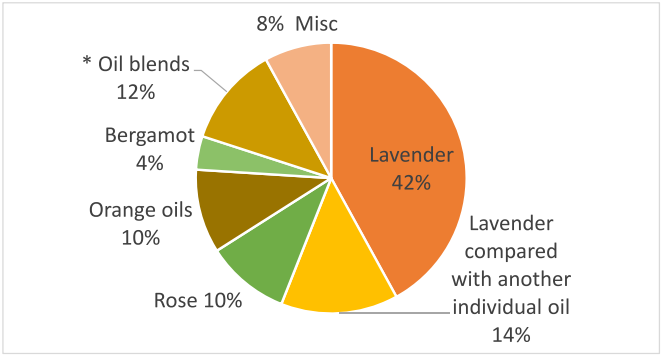

Fig. 4. Choice of essential oils for intervention in 50 RCTs
*Oil blends: A blend of essential oils used as one test intervention containing up to 4 different essential oils.

(3) Room diffusion

Room diffusion of essential oils in a water vapourised diffuser has been used in research studies to measure its impact of the level of anxiety experienced by patients during dental treatments, in pre- and postoperative surgical procedures, and in obstetrics [57] with varying degrees of success [35,73,32]. Of the nine RCTs that used room diffusion, five reported an improvement in stress and anxiety [39,46,51,62,74] while the remaining four studies did not report a significant advantage from the aromatherapy intervention [47,57,70,75].

(5) Oxygen masks

Four studies in the review applied the essential oil to oxygen masks to assess the impact on pre- and postoperative anxiety. One trial reported an improvement in anxiety scores [66].

Three studies examining pain and procedural anxiety proved inconclusive [44,49,76].

3.3.4. Inhalation aromatherapy by patient population in RCTs

The RCTs reviewed were divided by patient population. These were:

Procedural anxiety (62%), obstetrics (16%), dental anxiety (12%), oncology (6%), anxiety related sleep issues (4%), as can be seen in Fig. 6 below.

(a) Procedural anxiety

There has been a growth in clinical studies examining the impact of aromatherapy as an alternative to pharmacological interventions to treat a wide range of procedural anxiety. Anxiety is frequently experienced by patients undergoing medical procedures. While stress levels are subjective and vary from patient to patient, for those awaiting surgery, anxiety, if undertreated, can frequently have a negative impact on recovery [22].

A holistic, more patient-centred approach using complementary therapy such as aromatherapy may be considered as a non-pharmacological strategy to reduce stress levels. RCTs were conducted for patients undergoing the following procedures: dialysis [63]; biopsy [72,73]; cardiac surgery [35,37,43,44,77,78]; urology [64]; orthopaedic surgery [71]; laparoscopy [78]; colonoscopy [59] and general surgery [2,79,31].

In 66% [21] of these trials a positive effect on anxiety levels during procedures was reported across a diverse range of applications using infused cotton/gauze, patches, aroma pendants, oxygen masks and room diffusion [2,35,36,44,59,61,75,80,81]. The remaining trials reported little or no improvement following the aromatherapy intervention. The mode of application or the choice of oil did not seem to influence the outcome of the trials. The majority of trials used Lavender oil (*Lavandula angustifolia*) as a single oil intervention or in some cases compared it to a second test group using another individual oil to assess their effect on the levels of anxiety [2,64].

Twelve of the studies examining procedural anxiety used physiological measures including salivary cortisol, blood pressure and heart rate [28,35–44,81] with eight of those demonstrating a favourable response from the aromatherapy intervention. However, in the *Journal of Reconstructive Microsurgery*, a study in the US by Shammas et al. (2021) conducted a randomised controlled trial with 49 oncology patients undergoing breast reconstruction surgery. In this study, four drops of lavender (*Lavandula angustifolia)* oil were placed on the patient's wrist and patients were asked to inhale the aroma while in the holding area prior to surgery with coconut oil used as a control. Four drops of lavender were placed on the temple of each patient by the anaesthetist during the surgery and by the nursing team post-surgery on a cotton ball 20 cm from the patient. The trial did not result in any measurable differences in blood pressure, respiratory rate or in the scores of the Hospital Anxiety and Depression Scale (HADS), the pain (Visual Analogue

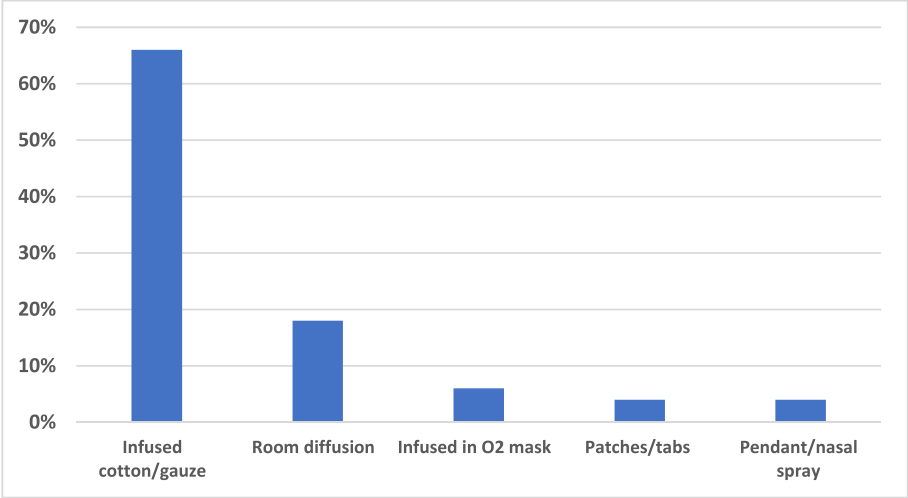

Fig. 5. Inhalation aromatherapy in 50 RCTs by mode of application.

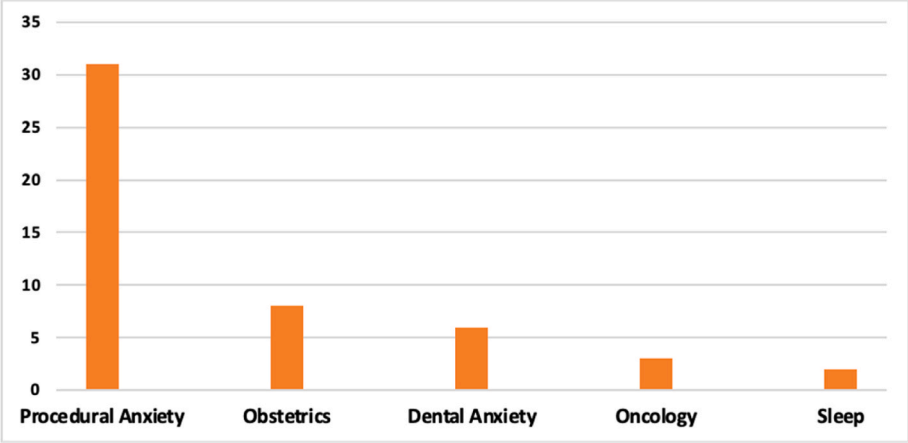

Fig. 6. Number of RCTs using inhalation aromatherapy by patient population 2000–2021.

Scale, VAS) or in the sleep (Richards–Campbell Sleep Questionnaire, RCSQ) measurements between the test and the control intervention. Despite this result the investigators stated that lavender oil was a "low-cost therapeutic that may be safely used in the postoperative management of the breast reconstruction patient" [80].

(b) Obstetrics

Aromatherapy has been used in obstetrics for over 30 years. In a UK evaluation study by Burns et al. (2000), its use in labour by 8058 patients was examined from 1990 to 1998. The report concluded that over 50% of mothers found aromatherapy beneficial. It also noted that in the period under review, the use of Pethidine had fallen from 6% to 0.2% [82].

In the current review, the inhalation aromatherapy clinical trials in obstetrics were conducted in Iran [7] and Japan [1]. These studies were conducted at various stages during labour and post-delivery up to 6 weeks to evaluate the impact of an essential oil intervention. Six studies used impregnated cotton ball or gauze for inhalation. In six of the eight studies there was a significant improvement in pain and anxiety scores by the participants such as STAI, VAS, HADS, DASS-21 POMS and the Fatigue Severity Scale (FSS). In 2020, Sarajou et al., in a double blind randomised controlled trial, used a blend of 5% of lemon *(Citrus limon)* and 5% of peppermint *(Mentha x piperita)* oils to study the effect on nausea and vomiting in 90 women at the early stages of pregnancy. The oil blend was infused in a cotton ball and inhaled deeply through the nose by patients when feeling nauseous over a four-day period. The patients were instructed to breathe in 3 times at a 3 cm distance from their nose and to repeat after 5 min if required. The effect on the level of nausea was assessed over a 24-h period using the Fatigue Severity Scale (FSS), and Pregnancy Unique Quantization of Emesis (PUQE-24).

The control contained propylene glycol as a base and a very low concentration of the oil blend for a mild aroma. The results reported a significant reduction in the intensity of nausea and vomiting in the aromatherapy group in the second, third or fourth day compared to the control group. No adverse side effects were reported [83].

In Iran in 2016, Sharipour et al., conducted at trial with 120 women to examine the effect of 2 different essential oils on post caesarean anxiety. One test group used 2 drops of sage (*Salvia officinalis*) essential oil and the second group, 2 drops of neroli (*Citrus aurantium* x L) essential oil. This was placed on the rim of the oxygen masks post-surgery. The control used sweet almond oil on the oxygen mask only. Using the STAI questionnaire the trial reported a reduction in anxiety in both test groups and concluded that aromatherapy was a non-invasive and cost effective method in aiding the reduction of post caesarean anxiety [84].

In a trial in Japan, essential oils containing high levels of linalool and linalyl acetate (bergamot *(Citrus bergamia)*, lavender (*Lavandula angustifolia)* and petitgrain *(Citrus aurantium)*) were used in room diffusion to investigate the potential anxiolytic effects of these chemical components

[57]. The study examined the physiological and psychological effect of inhalation aromatherapy on 13 pregnant women at week 28 of gestation. The results proved inconclusive given the small sample size and the fact the group was not blinded [57].

(c) Dental anxiety

Dental anxiety is a major concern as it is estimated that between 54% and 92% of dental patients suffer from anxiety which can affect both their treatment and recovery [67]. Recent systematic reviews have examined the use of aromatherapy and concluded that it can be of benefit during dental treatments [67,69].

In this current review, six randomised clinical trials were included using orange *(Citrus sinensis)*, lavender (*Lavandula angustifolia)* or roman chamomile *(Anthemis nobilis)* essential oils as the test intervention with the control receiving standard care. Four trials used room diffusion as an intervention [26,46,47,51,74]. The two remaining studies used a lavender infused patch which demonstrated a positive improvement in both, blood pressure and anxiety levels [26,48].

(d) Oncology

Oncology has been at the forefront of integrative medicine as the health profession seeks to develop a more holistic approach to patient care by combining conventional medicine with complementary treatments to act as a support to patients who face significant challenges throughout their patient journey [10,14,20,25,85,86].

In the last 20 years, aromatherapy as a complementary therapy has become a standard of care in cancer hospitals in the UK (The Christie, The Royal Marsden, St Guy's and St Thomas' hospitals). The practice was initially used as a support to nursing care but due to the positive patient and clinician feedback, it was fully integrated into patient care as a holistic practice. While much of the early evidence is anecdotal and limited in terms of design and methodology, aromatherapy continues to be offered to all cancer patients and is actively sought by them during their treatment [10,14,25,86,87]. St Guy's and St Thomas' hospitals in London offer a range of complementary treatments including inhalation aromatherapy via aromasticks, to patients during chemotherapy [87].

In this current review, 6% [3] of the trials were conducted with patients undergoing cancer treatment to alleviate the distressing side effects associated with chemotherapy and radiology such as anxiety, mood, nausea and insomnia [45,52,88]. All three trials used essential oil infused cotton balls/gauze for the intervention. In the *Clinical Journal of Oncology Nursing,* a trial was conducted in Turkey with 4 test groups: lavender (*Lavandula angustifolia)* essential oil, tea tree *(Melaleuca alternifolia)* essential oil, grapeseed oil *(Vitis vinifera)* and standard care only. The trial determined that the sleep quality and anxiety levels of chemotherapy patients improved after inhaling three drops of lavender essential oil placed on a piece of infused cotton nightly before sleep [88]. The other trials using similar methods concluded that there was no measurable advantage from the intervention but noted that the patients in the aromatherapy group were more relaxed and comfortable than the control group who received standard care only [45,52].

(e) Sleep

Sleep disturbance and increased fatigue can inhibit the recovery process. Lavender has been used widely for its anxiolytic properties and as mentioned in previous studies, it can help to alleviate the level of stress and anxiety associated with lack of sleep [89]. In one clinical trial an aromatherapy intervention was assessed to examine its impact on sleep and anxiety. In a Korean study, Lee et al. (2017), examined the effect of a blend of essential oils (lemon.

(Citrus limon), tea tree (*Melaleuca alternifolia),* eucalyptus (*Eucalyptus globulus*) and peppermint *(Mentha x piperita)* on sleep, anxiety and stress levels of young adults. In addition to the self-reporting anxiety scale, HRV was measured and blood samples were taken to measure immunoglobulin and levels of the stress hormone, cortisol. While there was no effect on the physiological measures, there was an improvement in sleep and stress amongst the participants [49].

A study in Brazil conducted by Polonini et al. (2020), used a blend of lavender (*Lavender angustifolia*) and fennel (*Foeniculum vulgare*) essential oils in a commercial nasal inhaler spray *Pinetonina®.* The intervention used two different concentrations of essential oils with a saline spray as a control over a three-month period. The higher concentration showed a significant improvement in sleep and a reduction in salivary cortisol levels [50].

3.4. Non-RCTs – pilot or feasibility studies

Clinical studies that are defined as pilot or feasibility studies have been included in this review if they have met the selection criteria. The primary objective was to evaluate the potential benefit if any, of introducing inhalation aromatherapy as a non-pharmacological intervention to alleviate levels of patient anxiety. They were not registered as a randomised controlled trial and for the purpose of this review were referred to as non-RCTs. These studies are frequently conducted at the initial stage of an investigation as a precursor to a clinical trial. Feasibility studies can be a cost effective method to assess the suitability of a proposed intervention while pilot studies are often similar in design and methodology to an RCT but on a smaller scale [20]. These non-RCTs have the advantage of developing or modifying potential strategies that can improve the quality of a subsequent clinical trial and act as a learning tool for a larger trial. While potentially beneficial, results from a small sample size can be misleading and overestimate the efficacy of an intervention. Twenty-six non-RCT clinical studies using inhalation aromatherapy were selected for review with a total of 1858 participants. They were conducted across nine countries, including USA with 38% [10] of the studies, Turkey 19% [5] Japan 15% [4], Germany 8% [2] and one study conducted in each of the following countries: Taiwan, Korea, Spain, Malaysia and Singapore. Over half of the studies took place within the last five years and over 75% since 2011 (see Fig. 7).

3.4.1. Outcome measurements used in Non-RCTs

The non-RCT clinical studies in this current review used a broader range of measurement tools to those in the randomised controlled trials in assessing the effects on stress, anxiety, fatigue, pain, mood and wellbeing. Some tools were also used in the RCTs and the most frequently included: The Visual Analogue Scale (VAS) in 22% of the non-RCTs, Spielberger's State-Trait Anxiety Scale (STAI) in 19%, and Profile of Mood States (POMS), in 7% of the non-RCTs.

The other measures accounted for 52% and included:

Beck Anxiety Inventory (BAI).
Chronic Stress and Burnout Scale (CSBS).
D2 Cognitive Test.
Fatigue Severity Scale (FSS).
General Anxiety Scale (GAD).
Hamilton Anxiety Measurement (HAM-A/D).
National Comprehensive Cancer Network (NCCN) Distress Thermometer.
Numeric Rating Scale (NRS).
Pittsburgh Sleep Quality Index (PSQI).
Postoperative Nausea and Vomiting (PONV).
Quality of Life (QOL).
The Mood and Wellbeing Checklist (MWC).
Verbal Descriptive Scale (VDS).

In addition to the stress and anxiety scales of measurement, 8 of the non-RCTs in this review measured vital signs at various time points during the study. This included heart rate variability (HRV), blood pressure, pulse rate and salivary cortisol.

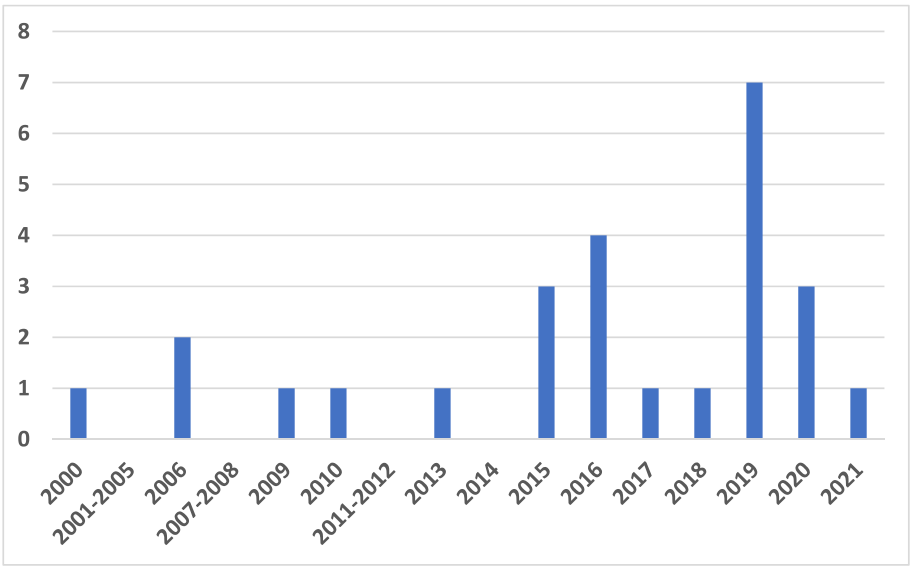

Fig. 7. Number of Non-RCTs using inhalation aromatherapy conducted between 2000 – 2021.

3.4.2. *Choice of essential oils in Non-RCTs*

The choice of essential oils used in the non-RCT studies is shown in Fig. 8 below. As can be seen the percentage and the choice of oils are similar to those used in the RCTs. With the exception of rose (*Rosa damascena)* oil predominantly used in the Iranian and Turkish RCTs, as it is an indigenous flower and widely used in cultural practice and plant medicine.

3.4.3. *Mode of application of aromatherapy intervention in Non-RCTs*

The non-RCT clinical studies differed from the RCTs in the method of essential oil application. Rather than the frequent use of infused cotton and gauze as an inhalation method, aromasticks were used by 26% [7] of the non-RCT studies. The breakdown by mode of application can be seen in Fig. 9 below.

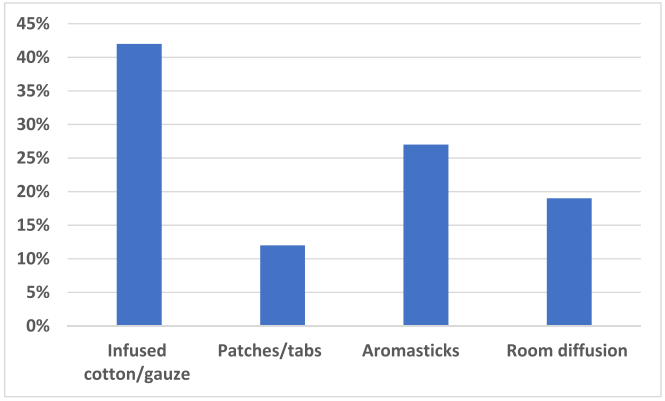

Fig. 9. Inhalation aromatherapy in non-RCTs by mode of application.

(1) Essential oil impregnated cotton ball/gauze

Fewer of the non-RCT studies (42% compared to 66% RCTs) used essential oil infused cotton ball or gauze for inhalation purposes as an aromatherapy intervention. As in RCTs, the essential oil infused item was frequently attached to the collar of the patient's gown or inhaled by the patient for a period of time. However, as was the case with many of the RCTs analysed earlier, the quantity of essential oil administered varied considerably making it difficult to evaluate with any degree of accuracy.

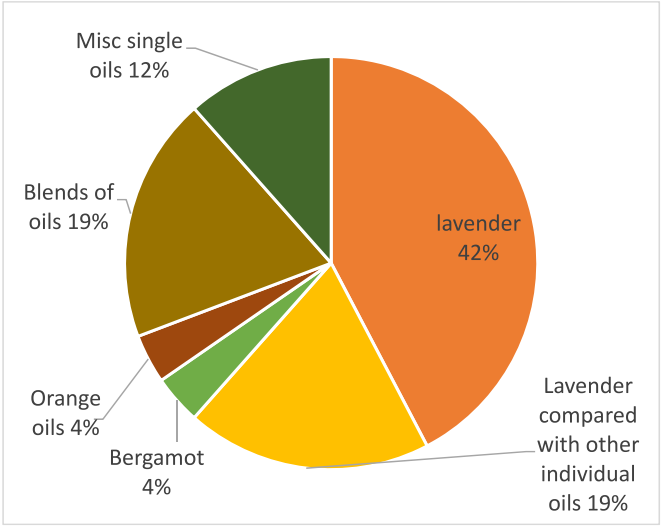

Fig. 8. Choice of essential oils for intervention in non-RCT clinical studies.

(2) Aromasticks

An aromastick is a nasal inhaler/stick containing the essential oil or blend of oils sealed in the stick and is considered a safe mode of application for individual use. In UK cancer hospitals, interventions using aromasticks are in widespread use amongst patients and were introduced in 2005 as a nurse driven intervention. They are now in widespread use in UK and USA in oncology settings as well as in hospices and have proved to be a beneficial and non-invasive self-management tool for patients. Some patients can be sensitive to aroma during chemotherapy and the aromastick has the added advantage that the aroma is not infused into the air generally, but is for personal use by the individual [14,25,86,87,90,91]. Aromasticks were used to investigate the effect of aromatherapy in non-RCTs in a variety of conditions including stress, anxiety, insomnia, postoperative nausea, and cognitive performance [13,91–96].

Three of the non-RCT studies used commercially manufactured brands. *AromaStick*® (marketed worldwide), *QueaseEase*® and *AetheroStick*® (both marketed in the USA) which contain a blend of essential oils [13,93,94]. For all three products a positive improvement on anxiety

levels was reported.

Aromasticks were not used in any of the randomised clinical trials included in this review.

(3) Aromatherapy patches and tabs

As reviewed earlier in the RCTs analysis, an aromatherapy patch or aroma tab is infused with an essential oil or combination of oils and is a commercially manufactured product. The patch or tab is attached to the patient's gown to allow for inhalation of the aromatic oil for the period of intervention. Three brands marketed in the US, *Elequil®*, *Bioesse®* and *Natural Patches of Vermont* were used in the non-RCT studies, two of which proved to have a beneficial effect on patient anxiety on procedural anxiety [97,98], while the third study reported no statistical significance [30].

In Wotman et al., 100 patients awaiting otolaryngologic surgery used a lavender infused *Elequil®* aroma tab [98]. The aroma tab was attached to the patient's gown or beside their pillow. The aromatherapy group was given two options, a minimum or maximum scent release depending on preference. The control group received standard nursing care. Wotman et al. concluded that while the lavender aromatherapy reduced anxiety in the patients, the effect was modest. There were limitations in the study as it was non-blinded, and it used a non-randomised sample group that introduced an element of bias, thus limiting the findings.

In many studies, the control group is standard care rather than the use of an alternative aroma or another essential oil. Doyle et al. (2020), carried out a study using a lavender infused patch and a jojoba oil as control in pre-operative patients awaiting biopsy in radiology. However there was no measurable difference between the test and the control which used VAS as a validated tool [30]. It is noted that some bias is likely to have occurred as the control, jojoba oil (*Simmondsia chinensis*), is odourless and easily detected by the control group which could affect the overall result.

(4) Room Diffusion

Room diffusion was used in 5 of the non-RCT studies to measure the potential benefit to levels of stress and anxiety in patients undergoing surgical treatment [99], the effect of bergamot *(Citrus bergamia) on the* parasympathetic nervous system [100], and stress inducing activities [12,101,102]. The results were encouraging in the reduction of stress levels but not reflected in physiological measures. One study did not report any significant advantage from the aromatherapy intervention [103].

(5) Oxygen Masks

One study in the USA in 2006, used two drops of 2% lavender essential oil in oxygen masks to assess its impact on anxiety and pain in breast biopsy surgery. The control was oxygen only. While the opioid requirements were the same in both groups, "*the patients in the lavender group reported a higher satisfaction rate*" [104].

3.4.4. Non-RCTs - inhalation aromatherapy by patient population

The non-RCTs were reviewed by patient population using the aromatherapy intervention (see Fig. 10). Unlike the RCTs seen earlier in this review, non-RCTs assessing the impact of inhalation aromatherapy did not include obstetrics and dentistry. The non-RCT studies were conducted in the following.

a) Stress and anxiety inducing conditions

Stress and anxiety have both physiological and psychological effects that can negatively affect health and quality of life. Twenty-seven percent [7] non-RCT studies in the current review examined the impact of inhalation aromatherapy across a broad range of situations and work environments including: measuring the levels of anxiety in a young student population [12]; student nurses undertaking end of year examinations [93]; on stress in a general population [91,101] and in staff "burnout" defined as "a prolonged response to chronic emotional and interpersonal stressors.'' [96].

In six of the seven studies the aromatherapy test group reported a positive effect on stress and anxiety scores [91,93,96,100,101,105]. A study in Japan [100], examined the use of bergamot essential oil on mood states and parasympathetic nervous system activity in 41 healthy females using room diffusion in three experimental groups: rest only, rest plus water vapour and rest plus bergamot oil in water vapour for 15 min. In the measurements of salivary cortisol levels and anxiety, both yielded a significant improvement. Three of the seven studies used a blend of essential oils in an aromastick [13,93,96], one a patch infused with the oil blend [105] and three studies used room diffusion [12,100,101].

b) Procedural Anxiety

In the non-RCTs reviewed, 65% [12] of the studies investigated the use of inhalation aromatherapy during various medical procedures including haemodialysis, colonoscopy, post-surgery anxiety and nausea, oral and cataract surgery. The aromatherapy intervention was administered using infused cotton/gauze, aroma tabs, patches, aromasticks or room diffusion. Seven of the studies used physiological measures including salivary cortisol, blood pressure and heart rate. A study of 75 patients in Singapore evaluated the effect of lavender (*Lavandula angustifolia)* essential oil on anxiety and vital signs before cataract surgery [99]. Patients were exposed to 20 drops of lavender oil in a room diffuser 20 min before the operation. On a different day, the control

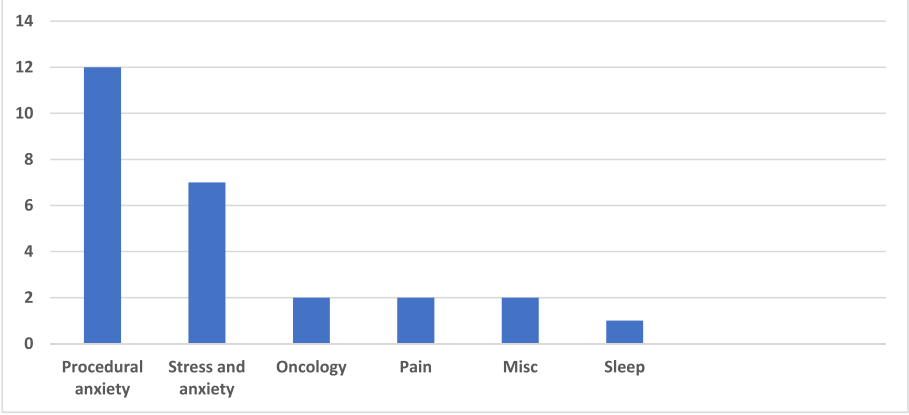

Fig. 10. Number of non-RCTs of inhalation aromatherapy by patient population 2000–2021.

groups' room was diffused with 20 drops of grapeseed oil before surgery. Anxiety levels and vital signs were measured before and after the intervention. The trial reported a statistical significance in the lavender aromatherapy group compared to that of the control in anxiety reduction in preoperative cataract surgery but only a slight reduction in the vital sign measures post intervention.

(c) Oncology

As highlighted earlier in this review, as a complementary treatment aromatherapy plays an active role in oncology, notably in chemo- and radiation therapy as a support to patients while they experience the distressing side effects associated with the treatment [10,14,20,25,85,86,106].

The two non-RCT studies were conducted with patients undergoing cancer treatment in an attempt to alleviate the challenging side effects such as anxiety, nausea and insomnia [95,107]. In a Malaysian study Lua et al. (2015), used gauze infused with ginger (*Zingiber officinalis*) essential oil secured in a pendant [107]. In the USA, Ohnikian et al. (2015), used lavender (*Lavandula angustifolia)* essential oil infused in an aromastick. Both studies concluded that there was no measurable advantage from the intervention but in the case of the aromastick study, the patients in the aromatherapy test group were more relaxed and comfortable than the control group post intervention [95].

(d) Sleep

Patients frequently suffer from sleep disturbance when undergoing clinical procedures which can heighten the level of anxiety with a negative impact on the recovery process [90]. Lavender essential oil has been used for its anxiolytic and sedative properties as illustrated in a non-RCT study in the USA which used a blend of 3 oils: lavandin *(Lavandula x intermedia),* bergamot *(Citrus bergamia)*and ylang ylang *(Cananga odorata*) essential oils for inhalation with post-surgery cardiac patients. It reported an improvement in sleep quality post intervention using the Pittsburgh Sleep Quality Index (PSQI) [108].

(e) Pain

Pain and the fear of pain can cause a high level of distress and anxiety during pre and postoperative surgery. Aromatherapy has been considered as a non-pharmacological intervention in an attempt to reduce opioid medication and ease the associated anxiety in patients. Two studies identified in the current review examined the effect of inhalation aromatherapy on pain [92,104].

Kim et al. (2006), carried out a study in the USA used one drop of lavender (*Lavandula angustifolia)* in an oxygen face mask with patients undergoing breast biopsy. While there was no significant difference between test and control post operative analgesics, patients reported a "*higher satisfaction rate with pain control in the lavender group*" [104].

Lindgren et al. (2019), in a study carried out in the USA, used a blend of oils from a commercial branded aromastick, *AetheroStick*® in 29 cancer patients. While the study was limited by its design and methodology, the conclusions stated that *"the research suggests that aromatherapy is a useful way to decreasing pain and anxiety scores when used in conjunction with standard medical care"* [92].

(f) Miscellaneous

Two studies examined the role of aromatherapy in measuring the olfactory response to stressful and demanding tasks [13] and cognitive performance [102]. Both studies reported a positive effect after the aromatherapy intervention. In the study by Schneider in 2016, a series of 3 armed randomised controlled experiments used the Swiss commercial product, *AromaStick*® containing 2 different blends of essential oils: "*Focus"* (peppermint (*Mentha x piperita*), rosemary *(Salvia rosmarinus),* and cinnamon (*Cinnamomum verum)* oils) and "*Alert*" (lemon *(Citrus limon),* peppermint *(Mentha x piperita),* rosemary *(Salvia rosmarinus)*, grapefruit *(Citrus paradisi),* black pepper *(Piper nigrum)* and basil *(Ocimum basilicum)* oils. A test group of 45 participants inhaled the aromastick for two consecutive inhalations before each task. Using the validated d2 test to assess selective attention and concentration levels, both aromasticks yielded a greater response and outperformed the control group (with no aromastick) [13].

4. Discussion

This systematic review was conducted to investigate the effect of inhalation aromatherapy on levels of stress and anxiety in clinical settings. The search strategy initially retrieved 628 studies and through application of the selection criteria and removal of duplicates, this resulted in 76 studies for review. The 76 studies were conducted on a total of 6539 patients in 13 countries between the years 2000 and 2021. Of these, fifty were RCTs and the remaining twenty six were non-RCT clinical studies. The studies were predominantly single or double blind with the control being either an odourless oil, a base with a mild aroma or the provision of standard care. RCTs are registered clinical trials that randomly assign participants to a test and a control group to assess the safety and efficacy of a drug or medical device. RCTs require considerable funding and a large sample size to be of any statistical significance. In comparison, non-RCTs are pilot studies that explore the potential for an intervention and are similar in design and methodology to a larger RCT but on a small scale. Pilot studies have the advantage of being less costly than a full scale trial and can provide valuable insight into efficacy of the proposed intervention, refine the study design where appropriate and highlight any concerns or safety issues. However, the reporting of positive outcomes in a non-RCT, can be overestimated given the smaller sample size compared to a full scale, much larger clinical trial. In some cases, a non-RCT can investigate the feasibility or potential for the introduction of a clinical practice as is the case with a number of aromatherapy studies in the current review [92,93,98].

The 50 RCTs used inhalation aromatherapy as an intervention with a total of 4681 participants. They were conducted across 11 countries. Iran accounted for 58% of the trials, USA 14%, Turkey 6%, Japan, Taiwan and Korea each with 4%. There were single studies included from Germany, India, UK, Australia and Brazil. Over two thirds of the RCTs (62%) were conducted since 2017 and a total of 94% conducted in the last ten years (since 2012). Twenty six non-RCT studies using inhalation aromatherapy were selected for review with a total of 1858 participants. They were conducted across 9 countries, the USA accounted for 38% of the studies, Turkey 19%, Japan 15%, Germany 8% and one study conducted in each of the following countries: Taiwan, Korea, Spain, Malaysia and Singapore. Over half of the non-RCT studies took place within the last five years and over 80% since 2011.

There were many differences in the approach taken by each study: the type of intervention; choice of oil; dosage of essential oil; range of treatments and the duration of exposure to the essential oil. As a result of this high level of heterogeneity a meta-analysis was not appropriate and a narrative synthesis was produced.

All the studies in the current review used quantitative measurement scales to investigate the patient experience containing a series of short questions based on a Likert scale. The majority of these measurement tools have been tested repeatedly for reliability and validity in research studies [109]. In the case of anxiety, the most frequently used measurement tool was the Spielberger's State-Trait Anxiety Scale (STAI) [38,40,64]. Published in 1970, it consists of 40 questions that evaluate anxiety at two levels: the current state of anxiety (STAI- S) and the propensity for anxiety (STAI-T). Other studies used the DASS-42 and the shorter version, DASS-21 [47,63,79], a self-reporting scale measuring depression, anxiety and stress and is often used in research and by clinicians as part of an overall clinical assessment. Another frequently used tool is The Hospital Anxiety and Depression Scale (HADS) with 14

questions that measure general symptom of anxiety and depression in patients [78,80,110]. All STAI, DASS-21/42 and HADS, use negatively worded questions and this can influence the participant to provide a negative response. On the other hand, a positively worded questionnaire can encourage participation and completion, and is a factor to be considered when designing future aromatherapy studies. In the last 20 years new tools to evaluate the effect on patient mental wellbeing and quality of life have been included in clinical research. In 2006 in the UK, clinicians and complementary therapy teams developed questionnaires to evaluate the patient's concerns and wellbeing as a support during cancer treatment [111]. These person-specific measures evolved into the MYCAW® (Measure Your Concerns and Wellbeing) questionnaire, now used in clinical settings internationally [25,112,113]. Another measurement tool for wellbeing (published in 2006), is the Warwick Edinburgh Mental Wellbeing questionnaire (WEMWB). It uses positively worded questions and is recommended for use with interventions [114,115]. To date this has not been used in any peer reviewed aromatherapy studies but has potential to be included in future research.

Over twenty different essential oils were used in the analysed studies. They were used as: a single oil; a comparison with one or more oils; in a pre-prepared blend; or a commercially manufactured product containing a combination of essential oils. Lavender was the most frequently used essential oil in 42% of the RCTs and in 42% of the non-RCT studies and was also used as a comparative oil with other essential oils in 14% of the RCTs and 19% in the non-RCT studies. The other essential oils that featured prominently in the RCTs were orange oils 10%, rose 10% and bergamot 4% (see breakdown of essential oils in Figs. 4 and 8).

There is growing evidence that essential oils can have positive anxiolytic effects when used in the clinical environment [22,68]. Recent systematic reviews have examined its use in clinical settings as a non-pharmacological intervention with promising results [21–23,116,117]. It is clear from the majority of the studies in this review that aromatherapy is being actively considered by clinicians to develop a complementary treatment in patient care to alleviate the distress caused by medical procedures. Seeking a non-pharmacological approach that is safe and effective will offer a beneficial support to clinical care. However, the conclusions in many studies in this review raised similar issues of concern regarding poor design and methodology, selection and reporting bias, lack of double blinding and sample size. This can influence the quality of the study and limit the certainty of evidence.

Aromatherapy by its very nature, can be difficult to measure effectively, the olfactory response can trigger an emotion or an associated memory which is personal to the individual being exposed to the scent. In 2016, Herz examined the effect of odour invoked memory and its link to the neuropathway in the brain [9]. These studies concluded that such unique experiences may contribute to an improvement in psychological and physiological health and wellbeing. Other studies have examined the effect of the aromatic molecules of the essential oil on the autonomic nervous system (ANS) with a varying degree of success [11,28,57,105,118]. A study in Korea, a randomised group of patients with urinary incontinence were assessed prior to a urodynamic examination. The measures included blood pressure, heart rate, respiratory rate and salivary cortisol. The results concluded that the inhalation of the clary sage oil (*Salvia sclarea*) reported a significant decrease in all measurements compared to both the lavender and the control groups [28]. Another study in the USA [118] examined the effect of inhalation aromatherapy on mood, immune function and ANS. Two test groups were lemon (*Citrus limon*) oil and lavender (*Lavandula angustifolia*) oil and the control, an odourless water. The findings demonstrated that norepinephrine levels were elevated and the mood improved in the lemon oil test group compared the lavender and the control but at a modest level.

The level of distress in patients before undergoing MRI procedures has been investigated using the inhalation of essential oils in a recent study in China, where the use of lavender inhalation combined with music therapy was examined in 200 participants. The combination of both interventions had a positive effect on the STAI measures [119]. An earlier study in Germany did not report results of any significance other than an improvement in mood [120].

The key question is: How can aromatherapy be measured effectively? A promising development in the current review are the studies which examined both psychological and physiological effects of essential oils. Twenty seven studies (21 RCTs; 8 non-RCTs) in total, 24 of which were in the last 10 years, used additional quantifiable measures including salivary cortisol, heart rate variability, heart rate and respiratory levels. A majority of these reported an improvement in these physiologic measures which is encouraging [26,28,40,43,47,48,51,52]. Combining these results with a validated tool for psychological measurement provides more robust evidence and should be considered in future studies.

This review examined the various modes of application used for essential oil inhalation. A point of interest was the use of aromasticks, patches and tabs with a consistent dose of oils, which yielded positive results in a majority of cases. In 2016, Schneider used the commercial brand AromaStick® to conduct a number of studies examining stress levels using both qualitative and physiological measures such as heart rate and salivary cortisol [13]. It concluded that short "sniffs" of a concentrated dose within a short timeframe directly via the nasal passageway was the most effective route for inhalation aromatherapy compared to room diffusion where the oil is randomly diffused into the air. In addition, the participant is consciously breathing in the aroma which can contribute to a more relaxed state. This is worthy of consideration when designing future clinical research protocols.

The sample size of the studies in the current review ranged from 14 to 361 participants. One third of the RCTs were over 100 participants and the majority of studies had a sample size of between 40 and 60 participants. This made it difficult to produce results of any statistical significance. However, as aromatherapy is a relatively new modality to be researched in a clinical setting, investigational studies are smaller in scale than the traditional medical trials. What was interesting to note that even when the results did not prove statistically significant, a number of studies reported that the aromatherapy test group were more relaxed and comfortable post intervention and despite the statistical result, aromatherapy was recommended as a safe and cost effective method for use in clinical practice [36,45,52,80,95].

4.1. Limitations

4.1.1. Choice of essential oil used in the intervention

While lavender essential oil was used in the majority of studies in this review, some studies did not specify the precise botanical name of the essential oil used in the intervention. For example, there are 3 commonly used lavender oils with varying chemical constituents: *Lavandula angustifolia* (true lavender) which has a floral aroma and is the oil traditionally used for its anxiolytic properties; *Lavandula latifolia* also known as spike lavender has a camphorous aroma and contains 1.8 cineole; and *Lavandula x intermedia* (Lavandin) is a hybrid of the two lavender plants [6]. If research is to examine the use of a lavender essential oil in the treatment of stress and anxiety, the active components (linalool and linalyl acetate) in *Lavandula angustifolia* suggest that it is the more appropriate essential oil. A similar confusion occurred with the orange oils. Both petitgrain and neroli (orange blossom) are oils from the bitter orange tree, *Citrus aurantium* x L. In the studies reviewed, both oils are frequently referred to as *Citrus aurantium* despite having very different chemical components. Two of studies referred to the botanical name of *Citrus aurantium* but did not use the common names to differentiate the precise orange oil used in the intervention [64,66]. Other trials were very clear in their oil choice, the neroli oil was referred to as "orange flower" oil from the *Citrus aurantium*/bitter orange tree [38] or as *Citrus aurantium* - neroli [65]. Neroli is extracted from the blossoms of the bitter orange tree, and in comparison, contains low quantities of linalyl acetate. In no case was neroli referred to as it is commonly known, *Citrus aurantium* var. *amara* [6,7].

Petitgrain (*Citrus aurantium x* L) essential oil is produced from the

leaves and twigs of the bitter orange tree [1] and contains over 50% of linalyl acetate and approximately 35% of linalool similar to that in bergamot *(Citrus bergamia)* and lavender *(Lavandula angustifolia)*. All three of these oils were used individually in a room diffusion study in Japan to measure their physiological and psychological effect on pregnant women. This was one of the few studies where the participants chose their preferred oil for the intervention [57]. In complementary therapy units in UK Cancer hospitals, patients are frequently invited to select an oil or blend of their choice to help alleviate the side effects experienced during their cancer treatment [14,87]. These are provided on-site by clinical aromatherapists in the complementary therapy team. Patients who are sensitive to aroma are offered a blend of oils to relieve nausea and aid relaxation and a blend is less recognisable which helps to minimise the potential for negative odour association [10].

4.1.2. Dosage & safety

In this current review, the precise dosage of essential oil was rarely reported and varied considerably from 1% to 100% concentrations of the essential oil. There are standard guidelines for aromatherapy practitioners on the safety and percentage dosage of essential oil over a multiple of applications. These include a 2% concentration of essential oil for a healthy population, 1% for the compromised and the elderly, with a maximum of 5% in acute cases [1,121]. Few studies specified the exact weight in grams or millilitres and the majority used '2 or 3 drops' of essential oil, making it challenging to assess the results given the lack of consistency in dosage. This was apparent in a recent systematic review when a meta-analysis was conducted but could not provide clear evidence given the high level of heterogeneity. The need for a more homogenous study design was recommended [53].

The use of commercial products such as aromasticks [91,92,94,95], aromatherapy patches [97] and aromatabs [51,71,72] had the advantage that they were manufactured using a specific dose. For this reason, the use of an aroma patch or aromatab which is attached to a patient's gown is worthy of serious consideration in future studies and could be customised by a clinical aromatherapist and manufactured under licence. However, it must be noted that in none of the studies using a commercial brand was information provided on the % dosage of the essential oil in each of the product formulations. Inhalation of an oil impregnated cotton ball or gauze was used in over half the RCTs and in 42% of the non-RCTs. This may have been due to ease of preparation and administration by nursing staff, particularly in pre- and postoperative stages of procedures and in obstetrics, but the lack of uniformity in dosage and the cumbersome mode of application is an issue that needs to be addressed in future studies.

Safety is of major concern in the use of essential oil given that the molecules contained in the oils are inhaled through the nose and enter the bloodstream via the lungs. While few adverse effects were reported in the studies reviewed, the lack of a consistent dose of essential oils is of concern to the reviewer. In 2021, a study examined the effect of aromatherapy on nurse mood states and stress levels in a nurse's station. A dose of 2 ml of 100% lavender oil was used in a room diffuser over a 24 period with short 2-min breaks. A clinical aromatherapist would consider this to be a highly inappropriate dose of essential oil to use in room diffusion for such an extensive period of time. The safety guideline recommended for the use of room diffusion is a maximum of 60 min at any one period [121]. Given this high dose (2 ml = approximately 50–60 drops), and the long period of exposure via room diffusion, it is not surprising that this is one of the very few studies that reported side effects by participants with nine of the thirty-nine participants experiencing respiratory symptoms and headaches [122]. In 2021, a trial by Moradi et al., described a study in which 4 ml of *Citrus aurantium* essential oil (referred to as orange flower oil - neroli), absorbed on a cotton ball, was placed on a patient's collar and they were asked to breathe normally for an hour before undergoing coronary angiography. Again, this is a high dose of concentrated essential oil. The study reported a reduction in anxiety and in blood pressure in the test group and fortunately, no adverse effects were recorded [38]. A disturbing finding was that only three studies included in this review noted that guidance was sought from an aromatherapist regarding choice and recommended dose of essential oil [49,52,108].

Few studies recorded the source of supply, batch numbers and safety data associated with the essential oil (s) used in the intervention. A number of RCTs particularly those in Iran [64,65], Turkey [48], Germany [26] and USA [72] did specify the data of the relevant oil supplier and one study referred to conducting gas chromatography [64]. The provision of this safety information is essential for the development of a comprehensive aromatherapy protocol which in turn, will ensure aromatherapy research is more scientifically based.

4.1.3. Bias

The element of a bias is a consistent issue arising in the clinical studies reviewed. It can be argued that it is difficult to blind both the nursing team administering the intervention and the patient, to a familiar recognisable aroma such as lavender and orange. Expectations and knowledge of aromatherapy can distort results and a pre-screening of participants is recommended in future studies that also includes anosmia. The COVID-19 pandemic resulted in many of those who contracted the virus to lose or distort their sense of smell which in some cases did not return for up to 18 months [123]. A small number of studies in the current review used this pre-screening process which added to the overall quality of the studies [13,35,40,50,64,72,91].

A blend of oils is less recognisable and if formulated by a clinical aromatherapist at the correct dose would provide a more consistent and measurable intervention for the test and control group. It is to be noted that in the current review bias could not be avoided given that the control was invariably odourless (distilled water), or at most a very mild aroma such as jojoba (*Simmondsia chinensis) or* sweet almond oil *(Prunus Amygdalus dulcis)*. This can be easily detected by the control group and patients can lose interest which can affect participation and the quality of the overall result.

In this review, retrospective clinical evaluation studies were also examined from a number of UK and USA oncology and obstetric hospitals who offer aromatherapy to all patients undergoing treatment. It was reported that it was difficult to avoid bias in the patient responses because the aromatherapist has a 1:1 relationship with the patient and is responding to their individual needs when preparing a customised oil blend. In addition, these particular studies were primarily experiential with no control group as the complementary therapy is offered to all patients. A control group would necessitate restricting patients from receiving an aromatherapy treatment [10,25,82,86,90,124].

5. Conclusion

The results of this systematic review indicate that the number of studies in inhalation aromatherapy is growing exponentially. The review demonstrates that inhalation aromatherapy has potential as a beneficial therapeutic intervention in areas of treatment where patients have a high degree of stress and anxiety. However, the quality of design and methodology of studies reviewed is still limited by sample size, lack of knowledge in essential oils, inconsistency in dose, administration and the element of bias. In future studies, it is recommended that a standard protocol be developed for the design of clinical studies using inhalation aromatherapy as an intervention. This protocol should include precise dosage of essential oils guided by a qualified aromatherapist who would advise on the appropriate choice of oil for both test and control and the recommended dose. In addition, every study should specify the botanical name of the chosen essential oil, its source, batch number, profile of chemical constituents and relevant safety documentation. An aromatherapy protocol that forms part of a robustly designed, double blind controlled study with measurable outcomes will create the opportunity for sound evidence-based scientific research.

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Author contribution statement

Fiona Hedigan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Visualization; Roles/Writing - original draft; Writing - review & editing. **Helen Sheridan:** Conceptualization; Funding acquisition; Methodology; Resources; Supervision; Writing - review & editing. **Astrid Sasse:** Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

Declaration of competing interest

Fiona Hedigan is also employed by Fiona Hedigan & Associates Limited. She is conducting her postgraduate research as part of a collaboration agreement between the Enterprise Partner (Fiona Hedigan & Associates Limited) and Trinity College Dublin.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2023.101750.

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