TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 10, Issue 4, Autumn 2025

Review

Effect of *Citrus* × *aurantium* L. Aromatherapy on Anxiety: A Systematic Review and Meta-Analysis

Alieh Farabi[1,2], Hamid Ahanchian[3], Vahid Ghavami[4], Vahid Reza Askari[5], Ali Reza Derakhshan[6,7]*, Maryam Soleimanpour-Moghaddam[2]

[1]Department of Persian Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Clinical Research Development Unit of Akbar Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Department of Biostatistics, Social Determinants of Health Research Center, School of Heath, Mashhad University of Medical Sciences, Mashhad, Iran
[5]Patient Safety Research Center, Clinical Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[6]School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[7]Persian Medicine Network (PMN), Universal Scientific Education and Research Network (USERN), Tehran, Iran

Received: 23 Nov 2024 **Revised:** 24 Jan 2025 **Accepted:** 25 Jan 2025

Abstract

Anxiety is a common condition often treated with pharmacological agents that have side effects. Aromatherapy, a non-pharmacological method using plant-derived essential oils, offers a safer alternative. *Citrus* × *aurantium* L. (bitter orange), traditionally used in Persian medicine to treat anxiety, is of particular interest. This systematic review and meta-analysis evaluate the efficacy of *C. aurantium* aroma in reducing anxiety. A systematic review and meta-analysis were conducted following PRISMA guidelines to evaluate the effect of *C. aurantium* aroma on anxiety. Databases including PubMed, Cochrane Library, Scopus, ProQuest, Science Direct, and Web of Science were searched for relevant clinical trials. Studies were included if they were randomized controlled trials involving human participants, used inhalation aromatherapy with *C. aurantium*, and measured anxiety with the State-Trait Anxiety Inventory (STAI). Data extraction and bias assessment were performed by two independent reviewers. Statistical analyses were conducted using Meta in R software version 4.2.2. An initial search identified 445 potential studies. After removing duplicates (n=46), 399 unique studies were screened. We excluded 35 review articles and 348 unrelated articles, resulting in 16 articles for detailed examination. Seven studies met the inclusion criteria and were analyzed, involving 666 participants (333 in intervention groups and 333 in control groups). The analysis revealed a significant reduction in anxiety in treatment groups using *C. aurantium* essential oil or neroli oil compared to control groups, with a mean difference of -12.45 (95% CI: -20.90 to -3.99, p = 0.004). Subgroup analysis indicated that both oils significantly reduced anxiety compared to control groups, with no significant difference between them (Q=0.64, p=0.42). Inhalation aromatherapy using *C. aurantium* essential oil and neroli oil effectively reduces anxiety. Further research is needed to explore underlying mechanisms and long-term benefits.

Keywords: Anxiety; Aromatherapy; *Citrus* × *aurantium*; Persian medicine; Meta-analysis; Systematic review; Herbal medicine

http://doi.org/10.18502/tim.v10i4.20731

Citation: Farabi A, Ahanchian H, Ghavami V, Askari VR, Derakhshan AR, Soleimanpour-Moghaddam M. **Effect of *Citrus x aurantium* Aromatherapy on Anxiety: A Systematic Review and Meta-Analysis**. 2025;10(4): 429-437. http://doi.org/10.18502/tim.v10i4.20731

*Corresponding Author: : Ali Reza Derakhshan
School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Email: derakhshanar@mums.ac.ir

Introduction

Anxiety is a fearful feeling that develops when one is exposed to frightening or demanding circumstances, such as an exam, surgery, or a chronic disorder [1].

In other words, anxiety is a reaction to any psychological, physiological, or physical pressure that a person experiences and finds challenging to adapt to [2]. Anxiety, caused by various factors, can lead to serious consequences such as gastric ulcers and cardiovascular issues [1,2].

In the clinical landscape, the foremost strategies for addressing anxiety commence with lifestyle modifications, followed by the implementation of cognitive-behavioral therapy (CBT) and the prescription of pharmacological agents, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). However, current approaches to anxiety management exhibit inherent drawbacks, including the delayed onset of therapeutic effects (e.g., SSRIs, SNRIs, and buspirone) and the potential for habituation, abuse, and tolerance (e.g., benzodiazepines and pregabalin). Additionally, the administration of anxiolytic medications may lead to a spectrum of adverse effects, encompassing amnesia, sedation, impaired concentration, depression, dependency, delirium, and withdrawal syndrome. Therefore, there is an urgent need for the development of anxiolytic interventions characterized by both safety and efficacy, tailored to address the complexities of subthreshold anxiety conditions [3].

Throughout history, non- pharmacological methods have been widely recommended as a preferable option for dealing with anxiety due to their fewer side effects and increased accessibility. Aromatherapy has gained significant attention in modern research as a notable non- pharmacological approach. Aromatherapy involves using essential oils derived from plants, either through applying them to the skin or inhaling them through the olfactory system. These oils play a dual role by addressing health issues and enhancing both physical and mental well-being. The use of plant-derived substances for therapeutic purposes dates back to medieval Persia, and the term "aromatherapy" was coined by Rene Maurice Gattefosse in the early 20th century [4]. Today, aromatherapy is popular worldwide, with research primarily focusing on its effectiveness in managing conditions such as depression, anxiety, muscle tension, sleep problems, nausea, and pain.

Aromatherapy garners appeal among both patients and healthcare practitioners due to its cost-effectiveness and limited incidence of adverse effects, while the extent of its therapeutic advantages remains a subject of ongoing debate. Typically, essential oils utilized in aromatherapy are derived from plant sources such as lavender, rose, lemon, bergamot, and various citrus varieties [5].

One of herbal medicines which has been employed in several aromatherapy and anxiety research is bitter orange (*Citrus* × *aurantium* L.). This plant has long been used therapeutically in traditional medicine. For example, in traditional Persian medicine, the aroma of this plant has a strengthening effect on the brain and nervous system, and it is specifically used to treat anxiety and induce happiness [6-8]. The essential oil obtained from the blossoms or fruit peel of this tree has been used in several clinical trial studies to reduce anxiety in different conditions.

The aim of this systematic review and meta-analysis is to evaluate the effect of *C. aurantium* aroma on anxiety. By synthesizing the available evidence, we aim to provide a comprehensive assessment of the efficacy of this intervention in reducing anxiety.

Material and Methods

Design

A systematic review and meta-analysis were conducted to assess the impact of aromatherapy employing *C. aurantium* oil on anxiety following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1).

Data Sources

The title/abstract/keywords fields of PubMed Central via PubMed, Cochrane Library, Scopus, ProQuest, Science Direct and Web of Science databases were systematically searched for eligible articles. We examined the references of articles obtained through database searches to discover additional pertinent articles. Unpublished studies were not included in the search strategy for this systematic review and meta-analysis.

Review Methods

Eligibility Criteria

The following study features are considered as eligibility criteria: (1) Population: clinical trials including human participants of any age, gender, and condition were included. (2) intervention: only inhalation aromatherapy with essential oil of any species of bitter orange fruit peel or blossom; (3) comparator: placebo; (4) outcomes: State-Trait Anxiety Inventory (STAI) scores; and (5) study design: randomized controlled trials (RCTs).

Excluded studies were studies with unanalyzable data, no control group, animal studies, and studies that assessed anxiety for longer than 30 minutes after intervention. Also, in the studies that had multiple of interventions and evaluations, we considered the score of the first intervention. In order to ensure assessment tool standardization, only studies employing the STAI

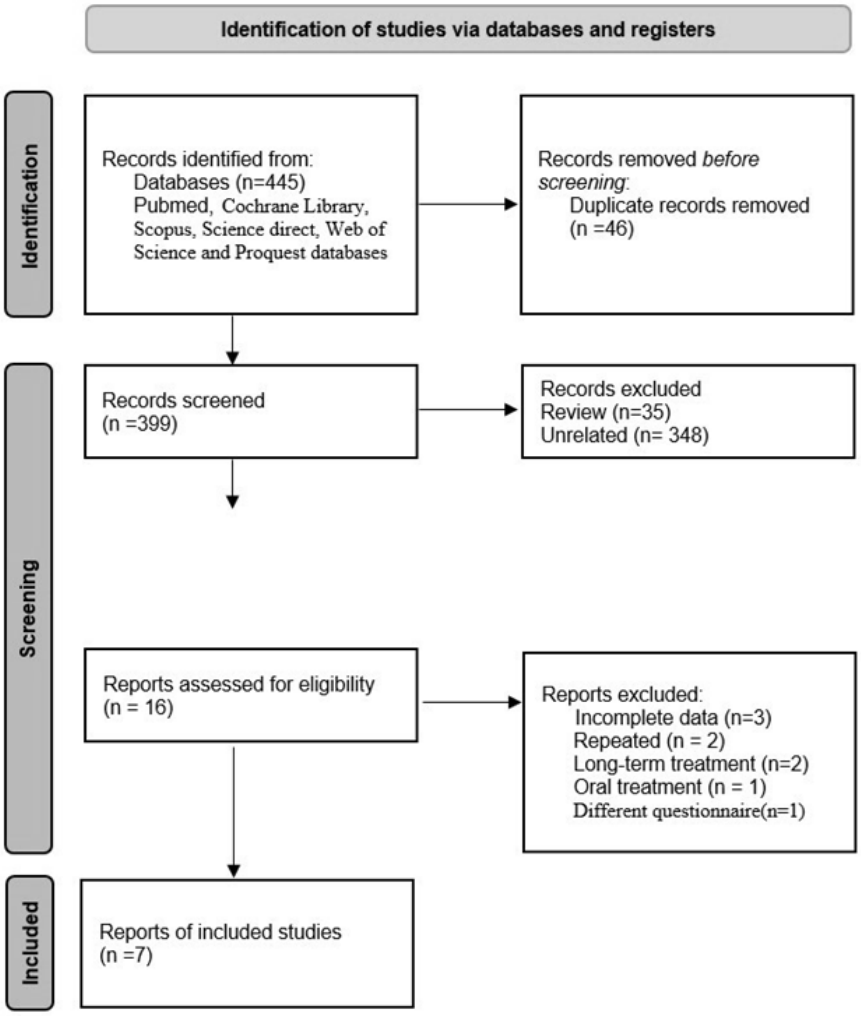

Figure 1. PRISMA flowchart of the study

scale were considered for inclusion in this systematic review and meta-analysis. Alternative assessment instruments were grounds for study exclusion. The STAI, encompassing both State Anxiety Inventory and Trait Anxiety Inventory subscales, provides a clear differentiation between transient state anxiety and enduring trait anxiety, rendering it a preferred choice for its precision and reliability in assessing anxiety within the scope of this study. The eligibility criteria for inclusion involve studies that are written in either English or Persian to October 10, 2023.

Search Strategy

We conducted searches in databases and reviewed references from identified articles up until October 10, 2023.

Cochrane: (*Citrus aurantium* OR bitter orange OR sour orange) AND (anxiety OR anxious OR anxiolytic) AND (Aromatherapy OR aroma OR inhalation) in Title/Abstract/Keyword

Scopus: "(TITLE-ABS-KEY (*Citrus aurantium* OR bitter orange OR sour orange) AND TITLE-ABS-KEY (anxiety OR anxious OR anxiolytic) AND TITLE-ABS-KEY (Aromatherapy OR aroma OR inhalation))".

Web of Science: "TOPIC:(*Citrus aurantium* OR bitter orange OR sour orange) AND TOPIC: (anxiety OR anxious OR anxiolytic)) AND TOPIC: (Aromatherapy OR aroma OR inhalation)".

ProQuest: scholarly Journals (*Citrus aurantium* OR bitter orange OR sour orange) AND (anxiety OR anxious OR anxiolytic) AND (Aromatherapy OR aroma OR inhalation).

ScienceDirect: (*Citrus aurantium* OR bitter orange OR sour orange) AND (anxiety OR anxious OR anxiolytic) AND (Aromatherapy OR aroma OR inhalation) in Title/Abstract /Keyword

There were no constraints on time or language.

An illustration of a PubMed search is provided in the table 1.

Study Selection and Data collection Process

Each of the two reviewers (ARD and AF) assessed eligibility on their own. When there was a disagreement,

Table 1. Strategy of search in PubMed

no	Searching term
1	*Citrus aurantium* (Title/Abstract/Keyword)
2	Bitter orange
3	Sour orange
4	1 OR 2 OR 3
5	Anxiety
6	Anxious
7	Anxiolytic
8	5 OR 6 OR 7
9	Aromatherapy
10	Aroma
11	Inhalation
12	9 OR 10 OR 11
13	4 AND 8 AND 12

the two reviewers discussed the issues and came to a resolution.

Data Items

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

Risk of Bias in Individual Studies

Two impartial assessors carried out the bias assessment. Based on the primary outcome STAI score using the modified Oxford quality scoring system (Jadad Score) for randomized trials (5). Reviewers discussed differences until they were addressed in accord. We evaluated the potential of bias using per protocol analysis as we prepared to quantify the impact of initiating and maintaining an aromatherapy intervention.

The Jadad scoring criteria for assessing risk of bias encompassed five key elements: (1) adequacy of randomization description, (2) appropriateness of randomization method, (3) implementation of double blinding, (4) adequacy of double blinding description, and (5) reporting of patient attrition. In cases where discrepancies were observed in the (1) randomization process and (2) blinding approach, a negative score was assigned. The cumulative Jadad score was calculated by summing these individual scores.

Statistical Analysis

We performed the meta-analysis using the package Meta in R software version 4.2.2 [9]. Since all of the studies had separately reported before and after intervention data for each group, we first calculated the mean change (MCwithin) and SD of the change from baseline to endpoint (SDwithin) for each group in each study. The formula used in this step was the following:

MCwithin = Meanendpoint – Meanbaseline

$$SD_{within} = \sqrt{[SD(baseline)]^2 + [SD(endpoint)]^2 - 2 * r * SD(basline) * SD(endpoint)}$$

where a correlation value (r) of 0.5 was used for computing SDwithin. In the following we calculated the effect size (EF) and its standard error (SE) as follow:

EF = MCwithin_Tretment - MCwithin_Control

$$SE = S_{pooled}\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

where, $n1$ represents the sample size in treatment group, $n2$ the sample size in control group, and S_{pooled} the pooled standard deviation of both groups. Using the SD_{within} of treatment group ($s1$) and control group ($s2$), the value of s pooled can be calculated this way:

$$S_{pooled} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

Heterogeneity across studies was evaluated by Cochran's Q test and I2[10]. The I^2 score values of 0% to 40% were considered not important [11]. Based on the results of Cochran's Q test and I^2 the effect sizes were pooled by using random effect model and were represented by a point estimate with a 95% confidence interval (95 % CI). Subgroup analyses were conducted based on drug (neroli oil and *C. aurantium* essential oil) and the difference between groups was evaluated by Q test. We had planned to employ funnel plots and both Egger's [12] and Begg's [13] tests to evaluate the publication bias but the limited number of studies did not allow this type of testing.

For targeted language refinement within specific sections of the manuscript, we employed ChatGPT 3.5, developed by OpenAI, via the OpenAI API. The language model was utilized for focused writing and grammar corrections, enhancing the precision and clarity of designated portions of the manuscript. The generated text was carefully reviewed and then integrated into the manuscript.

Results

Study Selection

In the initial phase of our systematic review and meta-analysis, a comprehensive search across pertinent databases yielded a total of 445 potentially relevant cases. After meticulous removal of duplicate entries (n=46), the dataset was refined to encompass 399 distinct cases. Subsequently, we conducted a rigorous

screening process to identify eligible studies, resulting in the exclusion of 35 review articles and 348 articles that were unrelated to the focus of our investigation. Among the remaining 16 articles, each article was thoroughly examined. Within this subset, three articles were deemed unsuitable for statistical analysis due to insufficient statistical data [14-16]. Furthermore, two articles emanated from clinical trials, and their data were found to be overlapping and hence, treated as duplicate sources [17, 18]. and[19, 20]. Additionally, two articles represented long-term research endeavors [21,22]. One article employed a questionnaire distinct from the STAI [23], and another included oral treatment intervention, rendering it incompatible with the primary analysis [24]. Ultimately, a total of seven articles were deemed eligible for inclusion and subsequently subjected to thorough statistical examination and analysis (Figure 1).

Study Characteristics

Characteristics of all included studies were summarized in table 2 and table 3. Methods and overview of the studies are as follows: 6 RCTs published in English from 2014 to 2021 [18, 25-29] and 1 RCT [19] published in Persian in 2015 were included in qualitative synthesis. Geographic origins of all the studies are Iran. In the meta-analysis, a total of 666 participants (333 cases in the intervention groups and 333 cases in the control groups) were analyzed.

The analyzed studies encompassed various populations, including patients undergoing surgery or angiography, individuals with acute myocardial infarction; conscious patients admitted to intensive care units, as well as post-cesarean women; and women in the first stage of labor. Patients within the intervention groups were administered the drug through inhalation methods, such as using a pad, gauze, cotton infused with the essential oil, applying the essential oil to the collar of their clothing, or affixing a patch to the inner wall of an oxygen mask. The control group received a placebo in similar way.

Quality Assessment

The Jadad scores of included studies are presented in the table 4.

Efficacy Assessment

Seven studies were analyzed ultimately. Mean difference between post-intervention anxiety change of the two groups was significantly different (EF= -12.45 (95% CI: -20.90, -3.99), p = 0.004). It means that the treatment (*C. aurantium* essential oil or Neroli oil) reduced anxiety more comparing to placebo (Figure 2). The result of subgroup meta-analysis showed that *C. aurantium* essential oil significantly reduced the anxiety more than control group; also, neroli oil reduced anxiety more compared to control group (Figure 2). There was no significant difference between *C. aurantium* essential oil or neroli oil (Q=0.64, p=0.42).

Discussion

Comprehending the neural foundation of anxiety, particularly the involvement of various neurotransmitters, is crucial for advancing the development of new anxiolytic medications. The main neurotransmitters involved in anxiety are gamma-aminobutyric acid (GABA), noradrenaline, serotonin, and dopamine. GABA is the major inhibitory neurotransmitter in the central nervous system, controlling neuronal excitability. It is predominantly found in the brain and helps regulate ongoing neuronal activity. GABA acts through ionotropic receptors ($GABA_A$ and $GABA_C$) and metabotropic receptor ($GABA_B$). Abnormalities in $GABA_A$ receptor function are associated with anxiety disorders, and benzodiazepines, which target $GABA_A$ receptors, are commonly used as anti-anxiety drugs. Serotonin also plays a role in anxiety, and SSRIs are recommended as first-line treatments. Some natural aromas have been shown to have anxiolytic effects, and their mechanism of action is believed to involve modulation of the GABAergic system, particularly $GABA_A$ receptors [18].

Non-pharmacological methods for managing anxiety offer several additional benefits, including more compatibility and a reduced risk of dependence [5].

Aromatherapy has gained increasing attention as a non-pharmacological approach for managing anxiety due to its perceived advantages of minimal side effects and enhanced efficacy. Aromatherapy encompasses the therapeutic application of essential oils, which can be assimilated into the body either through dermal absorption or via the olfactory system, facilitated by techniques such as massage or inhalation. These aromatic compounds, characterized by their volatility and molecular weight below 300 Da, engage the olfactory system, first dissolving into nasal mucous membranes and then binding to olfactory receptors [30, 31]. This process triggers action potentials within receptor neurons, initiating an electrical signal transmission to the olfactory bulb and subsequent processing in various brain regions, including the amygdala, hippocampus, orbitofrontal cortex, and thalamus, all closely associated with emotions [32]. Emerging evidence suggests that aromas may also directly impact neuronal receptors within the brain by crossing the blood-brain barrier [33]. Notably, aromatherapy has been linked to anxiolytic, anti-stress, relaxing, and sedative effects, potentially mediated through modulation of the GABAergic system, primarily $GABA_A$ receptors [34]. This mechanism aligns with findings from both animal and human studies, supporting the use of aromas and their constituents to alleviate anxiety-related symptoms and

Table 2. Summary of data extracted from included articles

Study (First Author)	Year	Study type	cont._ size	treat_ size	popula-tion	Time to apply int.	Duration of int.	drug	Drug Dose	placebo	placebo Dose	Type Treat
Sharifipour F	2015	Two-group randomized clinical trial study	40	40	post-ce-sarean	Im-medi-ately after pain onset	30 min	Ner-oli oil	3 drop 10% solu-tion	Normal saline	3 drops	Poured on a cotton swab ball & smell it for 5 min from 10 cm dis-tance
Namazi M	2014	Randomized clinical trial	63	63	First Stage of Labor	Be-fore inter-ven-tion	Dila-tions of 3-4	Ner-oli oil	4 mL of 8% solu-tion	Normal saline	4 mL	Gauzes im-pregnated were attached to the collar of the partici-pants
Moslemi F	2019	Dou-ble-Blind Placebo -Controlled Trial	70	70	acute coronary syndrome hospital-ized to ICU	Be-fore inter-ven-tion	20 min	Ner-oli oil	1.5 mL of 30% essen-tial oil in liquid paraf-fin	Food-grade liquid Paraffin	1.5 mL	Gauze at-tached to the collar of the pa-tient's clothes
Moradi K	2021	Sin-gle-Blind, Randomized controlled Trial	40	40	Patients Under-going Coronary Angiog-raphy	Be-fore inter-ven-tion	20 min after	Ner-oli oil	4 mL	Distilled water	4 mL	Diffused on a cotton wool pinned to the patient's collar
Karimza-deh Z	2021	Parallel ran-domized place-bo-con-trolled trial	50	50	conscious intensive care unit patients	Be-fore inter-ven-tion	Immedi-ately	*Cit-rus au-ran-tium es-sen-tial oil*	5 drops of 100% solu-tion	Normal saline	5 drops	Gauze were attached to the patient collar (10 cm distance) for 30min
Shirzade-gan R	2020	Triple-blind, randomized, controlled, clinical trial	40	40	Patients with Acute Myocar-dial in-farction	30 min be-fore	15-30 min after	*Cit-rus au-ran-tium es-sen-tial oil*	3 drops of 90% solu-tion	Sun-flower oil	3 drops	patches con-nected to the inside of the patients' ox-ygen masks for 20 min
Ebrahimi A	2021	Random-ized, sin-gle-blind, placebo-con-trolled clinical trial	30	30	patients in preop-erative period	Be-fore inter-ven-tion	20 min after	*Cit-rus au-ran-tium es-sen-tial oil*	2 drops of 100% solu-tion	Distilled water	2 drops	Poured on a napkin inhaled it for 20 min at a distance of 20 cm

Cont. size: control size; duration of int.: duration of intervention.

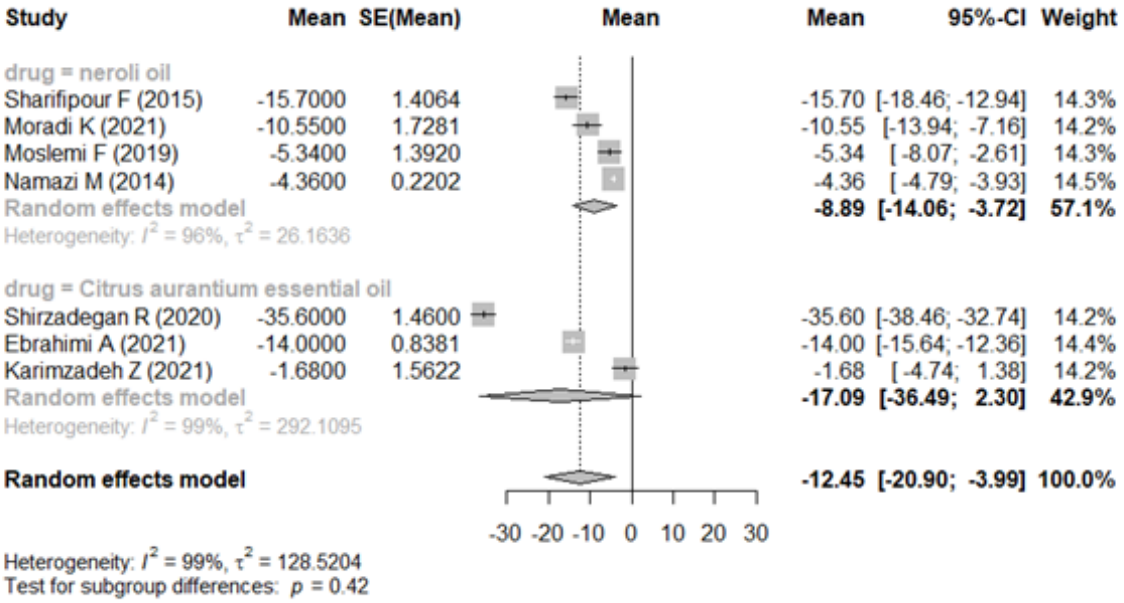

Figure 2. Pooled effects of aromatherapy on anxiety

Table 3. Results of included studies.

Study	Mcont_B	SDcont_B	Mcont_A	SDcont_A	Mtreat_B	SDtreat_B	Mtreat_A	SDtreat_A
Sharifipour F	62.48	5.67	60.23	5.37	62.20	5.617	44.25	7.8
Namazi M	61.86	1.327	56.38	1.128	55.16	1.247	45.32	1.216
Moslemi F	45.13	6.40	42.36	6.49	42.77	9.72	34.66	9.68
Moradi K	52.04	4.26	51.66	3.87	53.3	10.13	42.37	10.15
Karimzadeh Z	57.7	8.28	57.72	8.2	53.92	7.96	52.26	6.55
Shirzadegan R	59.52	7.47	57.27	6.58	61.37	6.86	23.52	3.28
Ebrahimi A	39.7	10.2	40.7	9.7	43.17	7.89	30.17	5.6

Mcont B: Mean of control group Before intervention; SDcont B: Standard Deviation of control group Before intervention; Mcont A: Mean of control group After intervention; SDcont A: Standard Deviation of control group After intervention; Mtreat B: Mean of treatment group Before intervention; SDtreat B: Standard Deviation of treatment group Before intervention; Mtreat A: Mean of treatment group After intervention; SDtreat A: Standard Deviation of treatment group After intervention

Table 4. Risk of bias assessment of the included studies (Jadad score)

Author (year)	Sharifipour F 2015	Namazi M 2014	Moslemi F 2019	Moradi K 2021	Karimzadeh Z 2021	Shirzadegan R 2020	Ebrahimi A 2021
Q1	○	○	○	○	○	○	○
Q2	○	○	○	○	○	○	○
Q3	●	●	○	○	●	○	○
Q4	●	●	○	○	●	○	●
Q5	○	○	○	○	○	○	●
Q6	●	●	●	●	●	●	●
Q7	●	●	●	●	●	●	●
Total	3	3	5	5	3	5	3

behaviors [35]. Furthermore, aromatherapy has been shown to reduce anxiety by reducing cortisol levels, increasing serotonin levels, and potentially releasing endorphins [25].

Bitter orange essential oil, derived from *C. aurantium*, a member of the Rutaceae family, is a frequently-utilized component in aromatherapy. This essential oil is extracted from *C. aurantium* blossom or peel through a distillation process. The chemical composition of *C. aurantium,* responsible for its therapeutic effects, encompasses vitamins, minerals, phenolic compounds, and terpenoids [36]. This essence is characterized by its bitter amber-colored liquid nature and a potent aroma, comprising approximately 35% hydrocarbons, 47% triphenyl alcohols such as linalool, triphenol, geraniol, nerol, flavonoids, and their acetates, along with 6% norolidol and 0.7% to 1.1% indole [28]. The essential oil of *C. aurantium* exhibits stimulating effects on the central nervous system and enhances neural connections [28, 36]. It serves diverse purposes, including anti-spasmodic, anti-inflammatory, anti-swelling, and blood pressure-regulating properties, and is known to address conditions such as depression, stress-related colic, stress dyspepsia, colitis, and skin disorders [26]. Its efficacy is comparable to fluoxetine in treating depression [28]. Notably, flavonoids, prominent phenolic compounds within this oil, act as benzodiazepine receptors, reducing anxiety levels. It has been shown that *C. aurantium*'s effect is akin to diazepam and can potentially serve as a substitute for the latter [28].

Linalool, a constituent found within bitter orange essential oil, is documented in scientific literature to exhibit a spectrum of pharmacological properties, including sedative, analgesic, anxiolytic, anticonvulsant, anti-inflammatory, and local anesthetic effects. It is hypothesized that one of the underlying mechanisms contributing to the observed effects of linalool involves the modulation of $GABA_A$ receptors [37]. Another potential mechanism responsible for the anxiolytic properties of bitter orange may be attributed to its geraniol content, as geraniol is also known to exert inhibitory effects on $GABA_A$ receptors [38].

The findings of this study suggest that incorporating aromatherapy with *C. aurantium* essential oil into nursing practice could provide a cost-effective and non-pharmacological option for managing anxiety in patients. Nurses can play a pivotal role in administering and educating patients about this complementary therapy, potentially enhancing patient comfort and well-being. Further training and integration of aromatherapy protocols in clinical settings may optimize patient care and offer an alternative to traditional pharmacological treatments for anxiety.

Conclusion

In this study, we conducted a comprehensive review of all clinical trials examining the impact of inhalation aromatherapy utilizing *C. aurantium* essential oil on anxiety, encompassing a total of seven articles [18,19,25-29]. Across all of these trials, aromatherapy interventions were administered within a timeframe of less than 20 minutes, with both experimental and control groups, and the resulting effects were promptly assessed using the STAI questionnaire. The results of the study indicated the positive effect of aromatherapy with *C. aurantium* essential oil on reducing stress.

Given that aromatherapy is a cost-effective and efficacious modality, and in light of the literature indicating the absence of reported adverse effects, it may be readily employed without concerns of potential side effects to ameliorate stress and anxiety across diverse medical scenarios and in daily life, especially when confronting stressful circumstances.

Conflict of Interests

The authors declare that they have no known competing interests.

Acknowledgements

This study is a part of PhD thesis of Dr. Alieh Farabi, which was done with the support of Mashhad University of Medical Sciences.

References

[1] Gong M, Dong H, Tang Y, Huang W, Lu F. Effects of aromatherapy on anxiety: A meta-analysis of randomized controlled trials. J Affect Disord 2020;274:1028-1040.

[2] Hur MH, Song JA, Lee J, Lee MS. Aromatherapy for stress reduction in healthy adults: a systematic review and meta-analysis of randomized clinical trials. Maturitas 2014;79:362-369.

[3] Kim M, Nam ES, Lee Y, Kang HJ. Effects of lavender on anxiety, depression, and physiological parameters: systematic review and meta-analysis. Asian Nurs Res 2021;15:279-290.

[4] Hasanshahi S, Parvizi MM, Bahreini M, Pouladi S, Mirzaei K. Investigating the effect of the aroma inhalation of orange and lavender essential oils in comparison with placebo on the level of anxiety in clients in a dental clinic in Shiraz: a double-blind controlled randomized clinical trial. J Med Plants 2020;19:295-309.

[5] Donelli D, Antonelli M, Bellinazzi C, Gensini GF, Firenzuoli F. Effects of lavender on anxiety: A systematic review and meta-analysis. Phytomedicine 2019;65:153099.

[6] Aghili MH. Naranj. Makhzan al-advieh. Tehran, Iran: Research Institute for Islamic and Complementary Medicine. 2008.

[7] Arzani MA. Andar Su-e Mezaj-e Del. Teb Akbari. Jalaleddin. Qom 2008; p 745.

[8] Tonekaboni MM. Naranj. Tohfat al-Momenin. Mostafavi Press. Tehran 1959; p 813.

[9] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153-160.

[10] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327:557-560.

[11] Higgins JJwc-ho. Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration 2011.
[12] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed) 1997;315:629-634.
[13] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-1101.
[14] Eslami J, Ebrahimi A, Hosseinkhani A, Khazaei Z, Darvishi IJBR. The effect of aromatherapy using Lavender (Lavandula angustifolia Miller) and Citrus aurantium L. extracts to treat anxiety of patients undergoing laparoscopic cholecystectomy: A randomized clinical trial in Iran. Therapy 2018;5:2096-2110.
[15] Pimenta FC, Alves MF, Pimenta MB, Melo SA, de Almeida AA, et al. Anxiolytic effect of citrus aurantium l. on patients with chronic myeloid leukemia. Phytother Res 2016;30:613-617.
[16] Chaves Neto G, Braga JEF, Alves MF, de Morais Pordeus LC, Dos Santos SG, et al. Anxiolytic effect of citrus aurantium l. in crack users. Evid Based Complement Altern Med 2017;2017:7217619.
[17] Namazi M, Amir AliAkbari S, Mojab F, Talebi A, Alavi Majd H, et al. Investigating the effects of aromatherapy with Citrus aurantium oil on anxiety during the first stage of labor. Iran J Obstet Gynecol Infertil 2014;17:12-19.
[18] Namazi M, Amir Ali Akbari S, Mojab F, Talebi A, Alavi Majd H, et al. Aromatherapy with citrus aurantium oil and anxiety during the first stage of labor. Iran Red Crescent Med J 2014;16:e18371.
[19] Sharifipour F, Bakhteh A, Mirmohammad Ali M. Effects of Citrus aurantium aroma on post-cesarean anxiety. Iran J Obstet Gynecol Infertil 2015;18:12-20.
[20] Sharifipour F, Mirmohammad Ali M, Hashemzadeh M. Comparison of the citrus arantium and salvia officinalis aroma impacts on post cesarean anxiety. Iran J Obstet Gynecol Infertil 2016;32:977-981.
[21] Mohaddes Ardebili F, Abdollahi F, Mobaderi T. The Effect of Aromatherapy with Bitter orange extract on anxiety and fatigue in type 2 diabetic patients. Adv Integr Med 2019;7.
[22] Moradi M, Niazi A, Mohammadi Payandar F, Jamali J, Arefadib N. The effect of aromatherapy with Citrus Aurantium essential oil on depression, stress and anxiety in pregnant women; a randomized controlled clinical trial. Taiwan J Obstet Gynecol 2025;64:512-518.
[23] Ahani N, Salehi K, Seidi J, Salehi B, Nouri. The effect of aromatherapy with Citrus aurantium on anxiety during MRI imaging in patients with spinal disorders: A randomized clinical trial. J Pharm Res Int 2019;26:1-8.
[24] Akhlaghi M, Shabanian G, Rafieian-Kopaei M, Parvin N, Saadat M, et al. Citrus aurantium blossom and preoperative anxiety. Rev Bras de Anestesiol 2011;61:702-712.
[25] Eslami J, Ebrahimi A, Darvishi I, Momeni K, Akbarzadeh M. Relaxation effects of aromatherapy intervention on female and male anxiety: a randomized control trial. Shirazeh Med J 2021;22.
[26] Shirzadegan R, Gholami M, Hasanvand S, Beiranvand A. The effects of Citrus aurantium aroma on anxiety and fatigue in patients with acute myocardial infarction: A two-center, randomized, controlled trial. J Herb Med 2020;21:100326.
[27] Karimzadeh Z, Azizzadeh Forouzi M, Tajadini H, Ahmadinejad M, Roy C, et al. Effects of lavender and Citrus aurantium on pain of conscious intensive care unit patients: A parallel randomized placebo-controlled trial. J Integr Med 2021;19:333-339.
[28] Moradi K, Ashtarian H, Danzima NY, Saeedi H, Bijan B, et al. Essential oil from citrus aurantium alleviates anxiety of patients undergoing coronary angiography: a single-blind, randomized controlled trial. Chin J Integr Med 2021;27:177-182.
[29] Moslemi F, Alijaniha F, Naseri M, Kazemnejad A, Charkhkar M, Heidari MR. Citrus aurantium aroma for anxiety in patients with acute coronary syndrome: a double-blind placebo-controlled trial. J Altern Complement Med 2019;25:833-839.
[30] Hartley N, McLachlan CS. Aromas Influencing the GABAergic System. Molecules (Basel, Switzerland). 2022;27:27082414.
[31] Sowndhararajan K, Kim S. Influence of fragrances on human psychophysiological activity: with special reference to human electroencephalographic response. Sci Pharm 2016;84:724-751.
[32] Fung TKH, Lau BWM, Ngai SPC, Tsang HWH. Therapeutic effect and mechanisms of essential oils in mood disorders: interaction between the nervous and respiratory systems. Int J Mol Sci 2021;22:22094844.
[33] Cui J, Li M, Wei Y, Li H, He X, et al. Inhalation aromatherapy via brain-targeted nasal delivery: natural volatiles or essential oils on mood disorders. Front Pharmacol 2022;13:860043.
[34] Hartley N, McLachlan CS. Aromas Influencing the GABAergic system. Molecules 2022;27:2414.
[35] Salehi-Pourmehr H, Ostadrahimi A, Ebrahimpour-Mirzarezaei M, Farshbaf-Khalili A. Does aromatherapy with lavender affect physical and psychological symptoms of menopausal women? A systematic review and meta-analysis. Complement Ther Clin Pract 2020;39:101150.
[36] Suntar I, Khan H, Patel S, Celano R, Rastrelli L. An overview on citrus aurantium l.: its functions as food ingredient and therapeutic agent. Oxid Med Cell Longev 2018;2018:7864269.
[37] Milanos S, Elsharif SA, Janzen D, Buettner A, Villmann C. Metabolic products of linalool and modulation of gaba(a) receptors. Front Chem 2017;5:46.
[38] Medeiros K, Dos Santos JR, Melo TCS, de Souza MF, Santos LG, et al. Depressant effect of geraniol on the central nervous system of rats: Behavior and ECoG power spectra. Biomed J 2018;41:298-305.