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Citrus aurantium Aroma for Anxiety in Patients with Acute Coronary Syndrome: A Double-Blind Placebo-Controlled Trial

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Abstract

Objective: This study evaluated the antianxiety effect of *Citrus aurantium* aroma (neroli oil) inhalation on patients with acute coronary syndrome (ACS).

Design: A double-blind, placebo-controlled randomized trial.

Setting/Location: This study was conducted in the Coronary Care Unit of Torfeh Hospital in Tehran, Iran, from September 2017 to February 2018.

Subjects: A total of 140 hospitalized ACS patients (mean age = 56.72 ± 11.38 years)

Interventions: Eligible patients were randomly assigned to citrus aroma and placebo groups to receive inhalation aromatherapy 2 days after hospitalization. Citrus aroma was 30% essential oil of *Citrus aurantium* L. flowers in paraffin, which was administrated three times a day. The placebo group received paraffin similarly.

Outcome measures: The rate of anxiety was measured at baseline and after intervention using the State–Trait Anxiety Inventory.

Results: At baseline, citrus aroma and placebo groups were similar in demographic characteristics as well as anxiety scores. After intervention, mean anxiety scores in the two groups become significantly different; the scores were 34.66 ± 9.6 and 42.36 ± 6.4 for citrus aroma and placebo groups, respectively ($p < 0.0001$). No side effect was observed.

Conclusions: According to the current findings, aromatherapy with *Citrus aurantium* L. aroma (neroli oil) may be a safe and efficient intervention and can be considered an easy and applicable method to reduce anxiety in patients with ACS.

Keywords: acute coronary syndrome, neroli oil, anxiety, *Citrus aurantium* L., aromatherapy, traditional Persian medicine

Introduction

Acute coronary syndrome (ACS), as acute myocardial ischemia, can lead to myocardial infarction (MI). ACS includes various conditions such as unstable angina, non-ST-segment elevation MI, and ST-segment elevation MI.[1] In the United States and European countries, ACS is the most common cause of death in cardiovascular diseases. In Iran, despite progress in using modern therapeutic methods, the ACS mortality rate shows an increasing trend.[2,3] Patients with ACS experience various environmental, physical, and emotional tensions during hospitalization in the cardiac care unit (CCU),[4,5] leading to high rates of anxiety increasing mortality in these patients.[6–8]

Therefore, prevention and treatment of anxiety in patients hospitalized in the CCU are an absolute necessity, otherwise it may lead to increase in extension and persistence of the disease, as well as risk of ischemia, second stroke, ventricular

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tachycardia, and fibrillation.[9,10] Benzodiazepines are one of the most frequently used antianxiety drugs, but occurrence of physical dependence and side effects such as anterograde amnesia and an increased risk of falling in elderly people are some adverse effects of these drugs.[11]

Therefore, there is a considerable tendency to use complementary and alternative medicine (CAM) to manage anxiety.[12] Aromatherapy is one of the CAM branches with a growing trend, particularly in nursing care.[13–15] Furthermore, in traditional Persian medicine (TPM), there is a considerable emphasis on using aromatic herbal drugs to relieve emotional disorders, including anxiety.[16,17] The traditional medicine in Iran (TPM) dates back to about 10,000 years, which generally emphasizes prevention and nonpharmacological therapies in the first step. It has provided many novel and effective therapies that are approved by new studies.[18–21] *Citrus aurantium* L. (CA) belongs to the Rutaceae family and its leaves, flowers, fruits peels, and seeds have various therapeutic uses.[22,23]

The essential oil of CA flowers has an exhilarant and mind tonic effect according to TPM.[24] It is also called neroli oil with significant antioxidant, anticonvulsant, and anti-inflammatory activities.[25–27] Several studies have indicated behavioral and anxiolytic effects of neroli oil inhalation as well as some effects on sleeping time, heart electrophysiological properties, and antidepressant activity after using the CA extract and essential oil in animal models.[28–31] Moreover, there are several clinical trials indicating antianxiety effects of CA. The usefulness for preoperative anxiety[32] and reduction of anxiety during labor,[33] as well as antianxiety effects in patients undergoing hemodialysis,[34] patients with chronic myeloid leukemia,[35] crack users,[36] and postmenopausal women,[37] are some examples.

Additionally, it was indicated that consumption of CA and oxazepam tablets had equal efficacy on preoperative anxiety in patients undergoing coronary artery bypass graft surgery.[38] There was no report of serious side effects while conducting the studies; therefore, it seems that the use of ordinary doses of CA derivatives is safe.[39,40] Following our recent study indicating the effectiveness of lemon balm in reducing anxiety of patients undergoing coronary artery bypass surgery,[41] the current study aimed to evaluate antianxiety effects of *Citrus aurantium* L. aroma inhalation on patients with ACS.

Materials and Methods

Participants

The study participants were patients with acute coronary artery syndrome hospitalized in the CCU and who satisfied entry criteria for inclusion in the trial. Participants provided written informed consent. Eligible patients were selected by the convenience sampling method and they were allocated to CA aroma and placebo groups through block randomization.

Inclusion and exclusion criteria

Inclusion criteria were as follows: a decisive diagnosis of ACS by a cardiologist, being a candidate for participating in the study and providing written informed consent, absence of serious psychological disorders and uncontrolled chronic diseases, lack of blindness or deafness, no smell and taste disorders, no history of allergy to citrus, no addiction, not using antianxiety drugs at least 1 day before intervention, and scores more than 20 according to the State–Trait Anxiety Inventory (STAI). The exclusion criteria were lacking willingness to continue participation in the study, occurrence of any serious cardiologic conditions such as cardiac shock and cardiopulmonary arrest, patient clearance, and transfer to another place.

Herbal drug preparation

CA aroma in this study was the essential oil of *Citrus aurantium* L. flowers. *Citrus aurantium* L. is the accepted name of a species in the genus Citrus and Rutaceae family (www.theplantlist.org). The citrus flowers were obtained from a garden in Chalus, Iran, and the essential oil was prepared by hydrodistillation and characterized by gas chromatography–mass spectrometry (GC/MS) analysis. CA aroma and placebo were prepared in the Traditional Medicine Clinical Trial Research Center of Shahed University. The CA aroma used for aromatherapy contained 30% essential oil of CA flowers in liquid paraffin, and the placebo was food-grade liquid paraffin (manufactured by Mehrabani Co.). Both the essence and placebo were poured and packaged in similar dark glass containers. A label showing the specific private code as well as instructions for use was attached on every container.

Study design

This double-blind, placebo-controlled, randomized clinical trial was conducted in the CCU ward of Torfeh Hospital in Tehran, Iran, from September 2017 to February 2018. The study followed guidelines of the Declaration of Helsinki for humans. All study participants provided written informed consent, and the study protocol was approved by the Medical Ethics Committee of Shahed University (IR. Shahed. REC. 1395. 172). In addition, the trial was registered in the Iranian Registry of Clinical Trials (IRCT2017011331919N1).

Randomization and blinding

Eligible patients were selected using the convenience sampling method and allocated to CA aroma and placebo groups through block randomization. The CA aroma and placebo had similar packages; they were randomly coded from 1 to 140. The codes were kept confidential by an independent pharmacist until the end of the study and data analysis. Aromatherapy was performed by a nurse who was uninformed about the study, and outcomes were recorded by another blind observer. The researcher and analyzer were blinded to allocation.

Intervention

The patients were examined under the supervision of a cardiologist and the eligible ones were included. After receiving a complete explanation of how the study was conducted, the participants signed the consent. Their demographic data were assessed and documented in related forms. Then, they were divided into two groups for receiving the standardized CA aroma or placebo. To perform intervention, first, a drop of CA aroma or placebo, prepared for the same patient with a special bar code, was rubbed over the nondominant hand's forearm and screened for 2 h. If the patient was not allergic, he/she entered the study. At the time of administration,

TABLE 1. GAS CHROMATOGRAPHY–MASS SPECTROMETRY ANALYSIS OF *CITRUS AURANTIUM* ESSENTIAL OIL IN COMPARISON WITH PHARMACEUTICAL STANDARDS

No.	*RT*	*%*	*Components*	*KI*	*Ph Eur limits (%)*
1	14.64	0.35	Myrcene	994	N/A
2	16.80	0.14	Limonene	1035	9.0%–18%
3	17.67	0.20	Z-β-Ocimene	1052	N/A
4	20.62	13.66	Linalool	1109	28.0%–44.0%
5	21.63	1.09	Phenylethyl alcohol	1129	N/A
6	22.34	0.13	*dihydro*-Linalool	1143	N/A
7	25.59	0.83	α-Terpineol	1209	2.0%–5.5%
8	25.76	0.2	γ-Terpineol	—	N/A
9	27.85	65.86	Linalyl acetate	1257	2.0%–15.0%
10	28.07	7.51	*cis*-Geraniol	1262	N/A
11	32.7	0.6	Benzoic acid, 2-amino-, methyl ester	1273	N/A
12	32.82	0.81	Neryl acetate	1366	Maximum 2.5%
13	33.70	0.90	Geranyl acetate	1386	1.0%–5.0%
14	—	—	β-Pinene	—	7.0%–17%
15	—	—	*trans*-Nerolidol	—	1.0%–5.0%
16	—	—	Methyl anthranilate	—	0.1%–1%
17	—	—	(E,E)-farnesol	—	0.8%–4.0%
		92.28	Total identified		

KI, Kovats Index; RT, retention time.

1.5 cc of the content inside the glass was applied to a small piece of gauze (2×2-cm square shape, same for every patient) and attached to the collar of the patient's clothes, and he/she was asked to breathe normally for 20 min.

Herbal drug assay

Results of the GC/MS analysis of citrus essential oil are shown in Table 1. As shown, the major components are linalyl acetate (65.86%), linalool (13.66%), and geraniol (7.51%). In addition, the range of compounds of the Neroli oil according to the European Pharmacopoeia standard is presented in a different column for comparison.

Data collection instruments

Demographic and clinical data, including age, gender, marital status, education, history of hospitalization, and history of smoking, were collected in a self-reported form before intervention. The patients' anxiety was measured

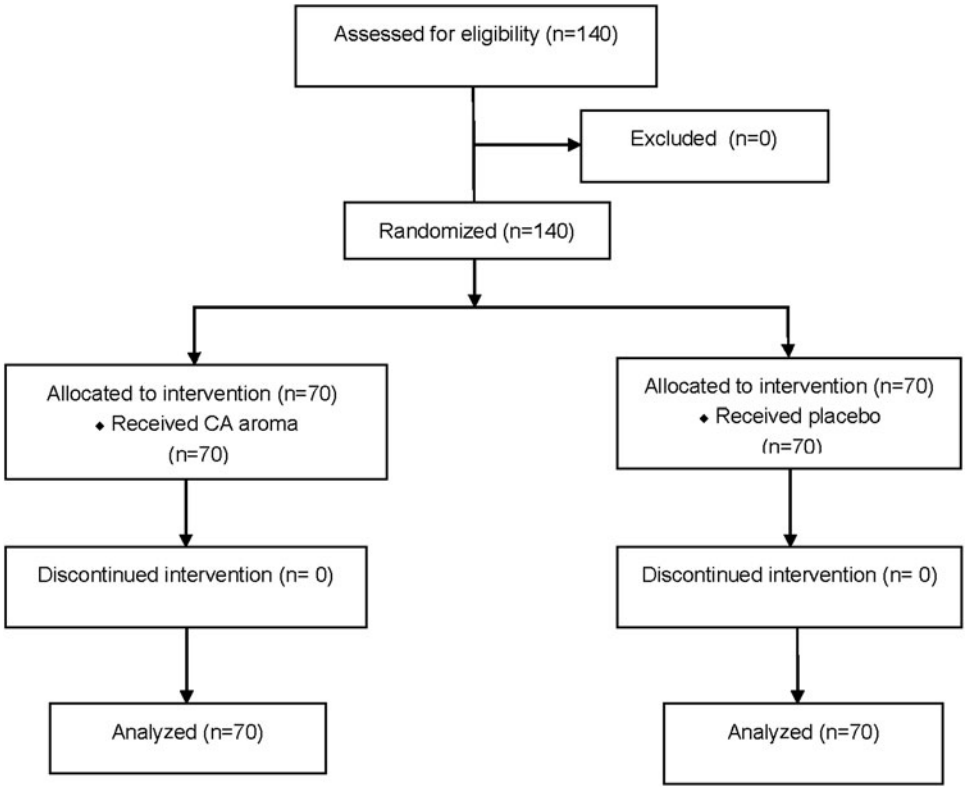

FIG. 1. CONSORT flow diagram of the trial. CA, *Citrus aurantium* L.

before and after the intervention using the STAI. This instrument is a self-report psychological inventory based on a 4-point Likert scale consisting of 40 questions. It measures two types of anxiety disorders: anxiety about an event and anxiety level as a personal characteristic, namely state anxiety and trait anxiety, respectively. The current study used the first 20 questions related to state anxiety.[42] A reliable and valid Persian version of STAI was used in the current study.[43]

Statistical analysis

The study data were analyzed using SPSS 18.0 (SPSS, Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to evaluate the normality of continuous variables. Continuous variables with normal distribution were analyzed using the *t*-test. Categorical variables were analyzed using the chi-square test and Fisher's exact test. *p*-Values <0.05 were considered significant.

Results

Participants

All the study participants ($n=140$) completed the trial. Figure 1 presents the flow diagram.

Evaluation of groups' homogeneity

Table 2 summarizes the patient demographic data. Obviously, there are no significant differences between the patients in both groups regarding age and other characteristic data such as gender, marital status, education, history of hospitalization, and cigarette consumption ($p>0.05$). Thus, the groups are homogeneous.

Table 2. Demographic and Clinical Characteristics of Participants

Variables	*CA aroma group (n = 70)* *Mean (SD)*	*Placebo group (n = 70)* *Mean (SD)*	p*
Age (years)	56.76 (11.39)	56.69 (11.37)	0.970
	n *(%)*	n *(%)*	
Gender			
Female	41 (58.6)	33 (47.1)	0.236
Male	29 (41.4)	37 (52.9)	
Marital status			
Single	3 (4.3)	4 (5.7)	0.240
Married	59 (84.3)	51 (72.9)	
Widow	8 (11.4)	15 (21.4)	
Education			
Illiterate	5 (7.1)	7 (10)	0.780
Primary	40 (57.1)	40 (57.1)	
Diploma	19 (27.1)	15 (21.0)	
University	6 (8.6)	8 (11.4)	
History of hospitalization			
Yes	40 (57.1)	38 (54.3)	0.865
No	30 (42.9)	32 (45.7)	
Smoking			
Yes	16 (22.9)	17 (24.3)	0.97
No	54 (77.1)	53 (75.7)	

*Statistical significance, $p<0.05$.
CA, *Citrus aurantium* L.; SD, standard deviation.

Table 3. Comparison of Anxiety Scores Between Groups Before and After the Intervention

Anxiety score[a]	*Group*	n	*mean*	*SD*	p*
Before intervention	CA aroma group	70	42.77	9.72	0.093
	Placebo group	70	45.13	6.40	
After intervention	CA aroma group	70	34.66	9.68	<0.0001
	Placebo group	70	42.36	6.49	

[a]Measured using the State–Trait Anxiety Inventory.
*Statistical significance, $p<0.05$.
CA, *Citrus aurantium* L.; SD, standard deviation.

Intervention

Effect of inhalation aromatherapy on anxiety. As Table 3 shows, the mean anxiety scores before intervention were 42.77 ± 9.72 in the CA aroma group and 45.13 ± 6.40 in the placebo group. There was no significant difference between the groups according to the independent *t*-test ($p=0.093$). The mean anxiety scores after intervention were 34.66 ± 9.68 in the CA aroma group and 42.36 ± 6.49 in the placebo group, and there was a significant difference between them ($p<0.0001$). The effect size was calculated as 0.8. No serious side effect was reported during the study.

Discussion

This study aimed to compare anxiolytic effects of CA aroma inhalation and placebo on ACS patients. The results showed a significant reduction of anxiety scores in the CA aroma group compared with the placebo group after intervention.

In line with the global approach to CAM, there is a growing trend in using inhalation aromatherapy as an easy and safe intervention to reduce anxiety in patients admitted to intensive care units.[44] According to TPM, aromatic herbal drugs had tonic and exhilarant effects on the heart. Therefore, they can not only improve psychological disorders such as anxiety and depression but also treat some conditions such as palpitation, as shown by a recent trial.[17] The influence of odorants on heart activity has also been shown in recent studies.[45]

Furthermore, the efficacy of aromatherapy on patients admitted to the CCU has been shown in several studies: anxiolytic effect of geranium (*Pelargonium graveolens* L'Hér; Family: Geraniaceae) essence on patients with acute MI,[46] essential oils of Damask rose flower (*Rosa damascena* Miller; Family: Rosaceae) and English lavender flowering tops (*Lavandula angustifolia* Miller, syn. *Lavandula officinalis* Chaix; Family: Lamiaceae) on patients undergoing open heart surgery,[47] and mixed essence of the blossom of the bitter orange tree (*Citrus aurantium* subsp. *amara* or *Bigaradia* Family: Rutaceae), chamomile (Matricaria chamomilla L., syn. *Matricaria recutita* Family: Asteraceae), and English lavender flowering tops (*Lavandula angustifolia* Miller, syn. *Lavandula officinalis* Chaix; Family: Lamiaceae) for sleep quality of patients with ACS,[48] are some examples.

The results of the studies by Najafi et al.[49] and Nematollahi et al.[50] are in line with our results; they indicated that

aromatherapy reduced anxiety in patients admitted to the critical care unit. However, the essential oil used in the two studies mentioned was of lavender and, in the latter, it was a combination (containing lavender, chamomile, and neroli), and in the case of the current study, it was neroli essence alone. To suggest a possible mechanism, the anti-inflammatory effect may be a common important mechanism. Recent studies have indicated that inflammation has an effect on behavior,[51,52] and extensive researches in this field have shown a bidirectional relationship between anxiety disorder and inflammation markers.[53]

Therefore, investigation into the effectiveness of anti-inflammatory treatments for the psychiatric disorder is a key topic for recent studies.[54,55] Regarding strong anti-inflammatory effects of CA essential oil and inhibition of production of nitric oxide, interleukin-6, tumor necrosis factor-α, and interleukin-1β, as well as their gene expression level,[56] the hypothesis can be developed that CA essential oil exerts anxiolytic effects mainly through its anti-inflammatory mechanism. The GC-MS analysis of CA essential oil used in the current study indicated the following main constituents: linalyl acetate (65.8%), linalool (13.66%), and geraniol (7.51%); however, another study conducted in Greece reported the following main constituents of CA essential oil: linalool (29.14%), β-pinene (19.08%), and limonene (12.04%).[57]

In addition, analysis of the flower essential oil obtained from CA cultivated in Tunisia reported the following main constituents: limonene (27.5%), (E)-nerolidol (17.5%), α-terpineol (14%), and α-terpinyl acetate (11.7%).[22] There is no doubt that changing the location or condition of the plant's growth will affect its essential components. Despite the lack of sufficient studies to determine the extent to which clinical changes in the components of essential oils can change its clinical effects, this should be considered in clinical studies using essential oils. Although this study has limitations such as the inability to reconcile the drug with the placebo, results suggest that the beneficial effects of aromatherapy with essential oil are considerable.

Conclusion

As the current study results indicate the effectiveness of inhalation aromatherapy with CA flower essential oil, it may be beneficial as an anxiolytic treatment for ACS patients. Considering the high prevalence and importance of anxiety among these patients and necessity of its management, this simple and efficient nursing intervention may be a valuable and important solution. Thus, it may be recommended that aromatherapy with CA essential oil be included in the nursing program of CCU patients.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Hinkle JL, Cheever KH. Brunner & Suddarth's Textbook of Medical-Surgical Nursing. New York: Lippincott Williams & Wilkins, 2013.
2. Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001;104:2855–2864.
3. Ahmadi A, Khaledifar A, Sajjadi H, Soori H. Relationship between risk factors and in-hospital mortality due to myocardial infarction by educational level: A national prospective study in Iran. Int J Equity Health 2014;13:116.
4. Hanssen TA, Nordrehaug JE, Eide GE, et al. Anxiety and depression after acute myocardial infarction: An 18-month follow-up study with repeated measures and comparison with a reference population. Eur J Cardiovasc Prev Rehabil 2009;16:651–659.
5. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med 2006;21:30–38.
6. Farquhar JM, Stonerock GL, Blumenthal JA. Treatment of anxiety in patients with coronary heart disease: A systematic review. Psychosomatics 2018;318–332.
7. Celano CM, Millstein RA, Bedoya CA, et al. Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis. Am Heart J 2015;170:1105–1115.
8. B esharat MA, Pourang P, Sadeghpour Tabaee A, et al. The relationship between coping styles and psychological adaptation in the recovery process: Patients with coronary heart disease. Tehran Univ Med J 2008;66:573–579.
9. Shen B-J, Avivi YE, Todaro JF, et al. Anxiety characteristics independently and prospectively predict myocardial infarctionin men: The unique contribution of anxiety among psychologic factors. J Am Coll Cardiol 2008;51:113–119.
10. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry 2008;65:62–71.
11. Uzun S, Kozumplik O, Jakovljević M, Sedić B. Side effects of treatment with benzodiazepines. Psychiatr Danub 2010;22:90–93.
12. Ravindran AV, da Silva TL. Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: A systematic review. J Affect Disord 2013;150:707–719.
13. Joswiak D, Kinney ME, Johnson JR, et al. Development of a health system-based nurse-delivered aromatherapy program. J Nurs Adm 2016;46:221–225.
14. Johnson JR, Rivard RL, Griffin KH, et al. The effectiveness of nurse-delivered aromatherapy in an acute care setting. Complement Ther Med 2016;25:164–169.
15. Scuteri D, Morrone LA, Rombolà L, et al. Aromatherapy and aromatic plants for the treatment of behavioural and psychological symptoms of dementia in patients with Alzheimer's disease: Clinical evidence and possible mechanisms. Evid Based Complement Alternat Med 2017;2017:9416305.
16. Avicenna The Canon of Medicine. Trans. Sharafkandi A. Tehran, Iran: Soroush Press, 2005:98. [In Persian].
17. Alijaniha F, Ghaffari F, Naseri M. Smelling drugs application, in the prevention and treatment of disease, from the

perspective of Iranian traditional medicine. Med Hist 2013; 5:67–77.
18. Ahmadi A, Mohagheghi M, Karimi M, et al. Anticancer effects of HESA-A in patients with metastatic colon cancer. Integr Cancer Ther 2009;1:71–74.
19. Hajiheydari MR, Yarmohammadi ME, Izadi P, et al. Effect of Nepeta bracteata Benth. on allergic rhinitis symptoms: A randomized double-blind clinical trial. J Res Med Sci 2017; 22:128.
20. Alijaniha F, Naseri M, Afsharypuor S, et al. Heart palpitation relief with *Melissa officinalis* leaf extract: Double blind, randomized, placebo controlled trial of efficacy and safety. J Ethnopharmacol 2015;164:378–384.
21. Soltanian AR, Mehdibarzi D, Faghihzadeh S, et al. Mixture of *Arnebia euchroma* and *Matricaria chamomilla* (Marhame-Mafasel) for pain relief of osteoarthritis of the knee—A two-treatment, two-period crossover trial. Arch Med Sci 2010;6:950–955.
22. Azhdarzadeh F, Hojjati M. Chemical composition and antimicrobial activity of leaf, ripe and unripe peel of bitter orange (*Citrus aurantium*) essential oils. Nutr Food Sci Res 2016;3:43–50.
23. Tripoli E, La Guardia M, Giammanco S, et al. Citrus flavonoids: Molecular structure, biological activity and nutritional properties: A review. Food Chem 2007;104:466–479.
24. Aghili Khorasani M. Makhzan-al-Advia. Tehran: Institute of Medical History, Islamic and Complementary Medicine, Iran University of Med Sciences, 2009:861.
25. Ammar AH, Bouajila J, Lebrihi A, et al. Chemical composition and in vitro antimicrobial and antioxidant activities of *Citrus aurantium* L. flowers essential oil (Neroli oil). Pak J Biol Sci 2012;15:1034–1040.
26. Khodabakhsh P, Shafaroodi H, Asgarpanah J. Analgesic and anti-inflammatory activities of *Citrus aurantium* L. blossoms essential oil (neroli): Involvement of the nitric-oxide/cyclic-guanosine monophosphate pathway. J Nat Med 2015;69:324–331.
27. Azanchi T, Shafaroodi H, Asgarpanah J. Anticonvulsant activity of *Citrus aurantium* blossom essential oil (neroli): Involvment of the GABAergic system. Nat Prod Commun 2014;9:1615–1618.
28. Khakpour S, Khosravi M, Mashayekhipour Z, Jahromy MH. Effect of *Citrus aurantium* L. essential oil and haloperidol on anxiety in male mice. World J Neurosci 2014;4: 427.
29. Leite MP, Fassin Jr J, Baziloni EM, et al. Behavioral effects of essential oil of *Citrus aurantium* L. inhalation in rats. Rev Bras Famacogn 2008;18:661–666.
30. Abbasnia VS. The effect of *Citrus Aurantium* flowers aqueous extract on sleeping time and the level of anxiety in mice. J Birjand Univ Med Sci 2016;23:307–314.
31. Costa CA, Cury TC, Cassettari BO, et al. *Citrus aurantium* L. essential oil exhibits anxiolytic-like activity mediated by 5-HT 1A-receptors and reduces cholesterol after repeated oral treatment. BMC Complement Altern Med 2013;13:42.
32. Akhlaghi M, Shabanian G, Rafieian-Kopaei M, et al. *Citrus aurantium* blossom and preoperative anxiety. Rev Bras Anestesiol 2011;61:702–712.
33. Namazi M, Amir Ali Akbari S, Mojab F, et al. Aromatherapy with *Citrus aurantium* oil and anxiety during the first stage of labor. Iran Red Crescent Med J 2014;16: e18371.
34. Kanani M, Mazloum S, Emami A, Mokhber N. The effect of aromatherapy with orange essential oils on anxiety in patients undergoing hemodialysis. J Sabzevar Univ Med Sci 2012;19:249–257.
35. Pimenta FCF, Alves MF, Pimenta MBF, et al. Anxiolytic effect of *Citrus aurantium* L. on patients with chronic myeloid leukemia. Phytother Res 2016;30:613–617.
36. Chaves Neto G, Braga JEF, Alves MF, et al. Anxiolytic effect of *Citrus aurantium* L. in crack users. Evid Based Complement Altern Med 2017;2017:8.
37. Choi SY, Kang P, Lee HS, Seol GH. Effects of inhalation of essential oil of *Citrus aurantium* L. var. amara on menopausal symptoms, stress, and estrogen in postmenopausal women: A randomized controlled trial. Evid Based Complement Altern Med 2014;2014:796518.
38. Kalani Z, Emtiazy M, Lotfi M, Dehghan K. Comparison of *Citrus aurantium* and oxazepam tablets efficacy on preoperative anxiety in patients undergoing coronary artery bypass graft surgery. JSSU 2015;23:1968–1975.
39. Stohs SJ, Preuss HG, Shara M. The safety of *Citrus aurantium* (bitter orange) and its primary protoalkaloid p-Synephrine. Phytother Res 2011;25:1421–1428.
40. Shara M, Stohs SJ, Mukattash TL. Cardiovascular safety of oral p-Synephrine (bitter orange) in healthy subjects: A randomized placebo-controlled cross-over clinical trial. Phytother Res 2016;30:842–847.
41. Spielberg C, Gorsuch R, Lushene R, et al. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.
42. Panahi-shahri M. Spielberger State-Trait test standardization among students in Isfahan (Persian) [MA thesis]. Tehran: Tarbiat-Modares University, 1994.
43. Ismaili M. A survey of the influence of Murita therapy on reducing the rate of anxiety in clients of counseling centers (Persian). Res Clin Psycho Counsl 2011;1:15–30.
44. Cho MY, Min ES, Hur MH, Lee MS. Effects of aromatherapy on the anxiety, vital signs, and sleep quality of percutaneous coronary intervention patients in intensive care units. Evid Based Complement Alternat Med.2013; 2013:381381.
45. Namazi H, Kulish VV. Fractal based analysis of the influence of odorants on heart activity. Sci Rep 2016;6: 38555.
46. Shirzadegan R, Gholami M, Hasanvand S, et al. Effects of geranium aroma on anxiety among patients with acute myocardial infarction: A triple-blind randomized clinical trial. Complement Ther Clin Pract 2017;29:201–206.
47. Ghasemi S, BabatabarDarzi H, Ebadi A. Comparison of the effects of aromatherapy with rose and lavender on physiological parameters of patients undergoing open heart surgery: A clinical trial. J Crit Care Nurs 2017;10:e10029.
48. Aalami H, Moghadam HM, Moghaddam MB, Bazeli J. Effect of hybrid aromatherapy on sleep quality of patients with acute coronary syndrome admitted to cardiac care unit. Middle East J Fam Med 2018;7:268.
49. Najafi Z, Taghadosi M, Sharifi K, et al. The effects of inhalation aromatherapy on anxiety in patients with myocardial infarction: A randomized clinical trial. Iran Red Crescent Med J 2014;16:e15485.
50. Nematollahi M, Bazeli J, Moghaddam M, Aalami H. Effect of aromatherapy on anxiety in patients with acute coronary syndrome hospitalized in cardiac care unit. Bali Med J 2017;6:331–336.

51. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 2012;37:137.
52. Lasselin J, Lekander M, Axelsson J, Karshikoff B. Sex differences in how inflammation affects behavior: What we can learn from experimental inflammatory models in humans. Front Neuroendocrinol 2018;50:91–106.
53. Glaus J, von Känel R, Lasserre AM, et al. The bidirectional relationship between anxiety disorders and circulating levels of inflammatory markers: Results from a large longitudinal population-based study. Depress Anxiety 2018; 35:360–371.
54. Miller AH, Raison CL. Are anti-inflammatory therapies viable treatments for psychiatric disorders? Where the rubber meets the road. JAMA Psychiatry 2015;72:527–528.
55. Müller N. Clinical trials of anti-inflammatory treatments of major depression. In: Baune BT, ed. Inflammation and Immunity in Depression. London: Academic Press, 2018:489–507.
56. Shen CY, Jiang JG, Zhu W, Ou-Yang Q. Anti-inflammatory effect of essential oil from *Citrus aurantium* L. var. *amara* Engl. J Agric Food Chem 2017;65:8586–8594.
57. Sarrou E, Chatzopoulou P, Dimassi-Theriou K, Therios I. Volatile constituents and antioxidant activity of peel, flowers and leaf oils of *Citrus aurantium* L. growing in Greece. Molecules 2013;18:10639–10647.

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