Efficacy of aromatherapy with *Rosa damascena* in the improvement of sleep quality of cancer patients: A randomized controlled clinical trial

Ghazaleh Heydarirad[a], Armaghan Sadat Keyhanmehr[a], Bahram Mofid[b], Hossein Nikfarjad[c], Seyed Hamdollah Mosavat[d,e,*]

[a] *Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[b] *Department of Clinical Oncology, Shohada-e-Tajrish Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[c] *ACECR (Academic Center for Education, Culture and Research), Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[d] *Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[e] *Research Center for Psychiatry and Behavior Sciences, Shiraz University of Medical Sciences, Shiraz, Iran*

1. Introduction

Sleep disorders are among the most common medical complaints in cancer patients. One of the outcomes of sleep disorders is their adverse effect on the quality of life and individual's social function. The results of previous studies show that sleep disorders in cancer patients are not regularly monitored or treated by health care providers and this can lead to an exacerbation of many of the patient's problems, such as fatigue, anxiety, depression, and eventually progression of cancer [1]. Based on statistics, 25–50% of all the prescriptions for cancer patients are hypnotic agents, the most prevalent of which are benzodiazepines. Drowsiness, dizziness, irritability, and amnesia are some side effects of these drugs, which are experienced by many patients, preventing them from taking the medication [2].

Nowadays, there is an increasing interest towards complementary and alternative medicine (CAM) [3,4], especially toward medicinal herbs [5,6]. This issue is related to the use of simple, safe, and effective therapeutic methods used to improve and optimize the quality of life, especially in cancer patients [7,8]. CAM methods help the patients to manage their problems with remedies with lower side effects and even lower socio-economic costs [9,10]. Moreover, various recent studies suggest that CAM methods such as acupuncture, aromatherapy, herbal medicine and yoga could improve the cancer patients' quality of life [11–14].

Aromatherapy is one of the CAM methods with a history of several thousand years [14,15]. Aromatherapy is used to treat various diseases through extracted essence of different parts of plants such as flowers, leaves and stems. Essences are volatile oils that have broad different dosage forms including inhalation, oral and topical ones [16]. The results of many studies suggest that aromatherapy is effective in improving the sleep quality [17–19].

Rosa damascene Mill (R. damascena) is a medicinal herb which is one of the most important species of the *Rosaceae* family [20]. This plant

has many antimicrobial, anti-AIDS, and anti-diabetes effects and has sedative and hypnotic properties [21]. The results of clinical studies have also shown sedative effects of *R. damascena* without any serious side effects [21,22]. In the traditional Persian references, for instance, the Liber Continens authored by Rhazes (865-925 AD) Canon of Medicine written by Avicenna (980-1037 AD) and the Storehouse of Medicaments by *Aghili Shirazi* (1670–1747 AD), it has been mentioned that *R. damascena* has sedative, analgesic, and cerebrotonic properties [23–25]. If *R. damascena* aromatherapy is effective in improving sleep disorders, it can be used as a complementary medicine in cancer patients, especially in those who prefer to take natural medicine. The value of this therapeutic modality is that it is not a systemic dosage form and does not interfere with the patients' routine drugs, so it can be useful, especially in patients who are on chemotherapy treatment.

Since previous studies have confirmed sedative and hypnotic effects of *R. damascena*, the present study aimed to examine the efficacy of *R. damascena* aromatherapy in the improvement of sleep quality in patients who suffered from cancer.

2. Materials and methods

2.1. Study design

This study was a randomized, single blind, controlled clinical trial which was designed with the aim of evaluating the effect of aromatherapy on the sleep quality of cancer patients. The subjects were selected among cancer patients referring to the oncology clinic of Shohadaye Tajrish Hospital, (Tehran, Iran); we used random sampling method and the inclusion criteria to select the patients.

2.2. Sample and sampling method

Initial interview with the cancer patients referred to the oncology

---

* Corresponding author. Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
  E-mail address: mosavath@sums.ac.ir (S.H. Mosavat).

clinic of Shohadaye Tajrish was done by the research physician. If they complained of sleep disturbance and had inclusion criteria, she explained the study purpose in detail and distributed the study questionnaires, and then enrolled them in the trial.

The inclusion criteria were being 18–65 years old, having cancer, not being satisfied with the sleep quality, having a normal olfactory function, and a life expectancy of more than 6 months. Exclusion criteria were willingness to withdraw from the study at any time; pregnancy; lactation; and suffering from asthma, dyspnea, chronic cough, and any possible sensitivity to Rosa essential oil.

The physician investigator enrolled the subjects using convenience sampling. Forty five eligible patients were randomized in three parallel groups. A statistician made a randomized list, using Number Cruncher Statistical System (NCSS: a statistical software) and simple block randomization method. Then, the enrolled participants were categorized into 9 blocks, each containing 6 participants. In the even number block, the first two participants were assigned to the *R. damascena* essential oil 10% group, the second two to the *R. damascena* essential oil 5% group, and the final two to the control group. In the odd number block, the first two participants were assigned to the *R. damascena* essential oil 5% group, the second two to the control group, and the final two to the *R. damascena* essential oil 10% group.

2.3. Intervention

The patients were randomly assigned to receive a 2-week course of nightly aromatherapy with Rosa essential oil in different dosages: 5% and 10% as the experimental groups, or no intervention as the control group. Patients in the experimental group were asked to keep the oil at room temperature and take it half an hour before going to bed (inhaled the oil for 20 min) for two weeks. The patients used 5 drops of *R. damascena* essential oil on a cotton ball which was held near their noses. The participants were asked to keep the cotton ball near their noses, so that it has a distance about 4–5 cm from their noses. Then, they smelled it for 20 min. All the outcome measures were evaluated at the beginning and the end of the intervention.

2.4. Drug preparation

The essential oil of *R. damascena* was purchased from herbal market in Ghamsar, Kashan (Iran). Then, the study drug was prepared by combining *R. damascena* essential oil with rapeseed oil and paraffin as the carrier in concentrations of 5 and 10%. Dropper bottle containing 10 ml essential oil was prepared for each patient.

2.5. Ethical considerations

The trial method was in compliance with the guidelines of the Declaration of Helsinki (1989 revision). This study was approved by the research deputy of the faculty of traditional medicine of Shahid Beheshti University of Medical Sciences (SBUMS), with the code of 904–1395. The trial protocol was registered in the Iranian Registry of Clinical Trials database with the reference number of IRCT2017070422865N2. Also, written informed consent form was signed by all of the enrolled participants.

2.6. Outcome measures

The primary outcome measure in our trial was changes in the scores of sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a widely used and validated 19-item self-report instrument on sleep disturbances experienced over the previous month [26]. Sleep latency and night sleep duration were the other primary outcome measures of this study. Any reported undesirable event was also considered as the secondary outcome.

2.7. Statistical methods

Demographic data and basic clinical characteristics of the participants are shown as the mean ± standard deviation for continuous variables or number (percentage). Normality of the continuous variables was checked, using Kolmogorov-Smirnov test. Wilcoxon Signed-Rank test was used to determine the changes in outcome measures before and after the intervention in each group. Kruskal-Wallis test was used to compare the effectiveness of the intervention among the three groups of the study. The Statistical Package for Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The significance level was set at < 0.05.

3. Results

3.1. Patients' enrollment

From October 2016 to June 2017, 72 volunteers were assessed for eligibility. Fifty four patients who met the inclusion criteria and agreed to participate in the trial were divided into three groups. Eighteen patients were assigned to the Rosa essential oil 5% group, 18 to the Rosa essential oil 10%, and 18 to the control group. Detailed description of the patients' enrolment, randomization and analysis is shown in Fig. 1.

3.2. Baseline clinical characteristics

The mean age in the control group was 50.20(± 18.54) years; in the essential oil 5% group and the essential oil 10% group, the mean age was 47.60(± 10.76) and 50.00(± 13.94) years, respectively. Among the male participants, 47% were in the control group, 18% in the essential oil 5% group, and 35% in the essential oil 10% group. Among the female participants, 25% were in the control group, 43% in the essential oil 5% group, and 32% in the essential oil 10% group. No significant differences were observed in the baseline characteristics among the three groups of the study (p value < 0.05) (Table 1).

3.3. Clinical response

In the experimental groups, the total Pittsburgh Index score showed a significant decrease (P < 0.05), but in the control group, there was no significant difference. Also, in the experimental groups, the time of sleep latency decreased significantly (P < 0.05), while in the control group, it slightly decreased (P = 0.593). In addition, in patients who used essential oil (5% and 10%), the sleep quality significantly improved compared with the control group after the intervention (P < 0.05). The mean duration of night sleep after the intervention also increased more in the experimental groups compared to the control group; this increase was not statistically significant (P = 0.224). However, the mean difference of the duration of night sleep before and after the study was significant [1.46 ± 1.57 and 1.80 ± 1.53 in the essential oil 5% group and in the essential oil 10% group, respectively compared to 0.36 ± 1.07 in the control group (P = 0.007)].

Although the effect of Rose essential oil 10% was shown to be better than 5% in the mean score of sleep quality, sleep latency, and mean duration of night sleep. The total Pittsburgh questionnaire scores of both groups (5% and 10%) were close, and their effects were significant in comparison with the control group. Table 2 displays the details of the changes of the study outcome measures before and after the study in each group.

3.4. Safety reports

R. damascena aromatherapy was well tolerated by the cancer patients. Only two patients discontinued the intervention due to headache and another one presented with frequent sneezing. Other participants did not report any adverse effect.
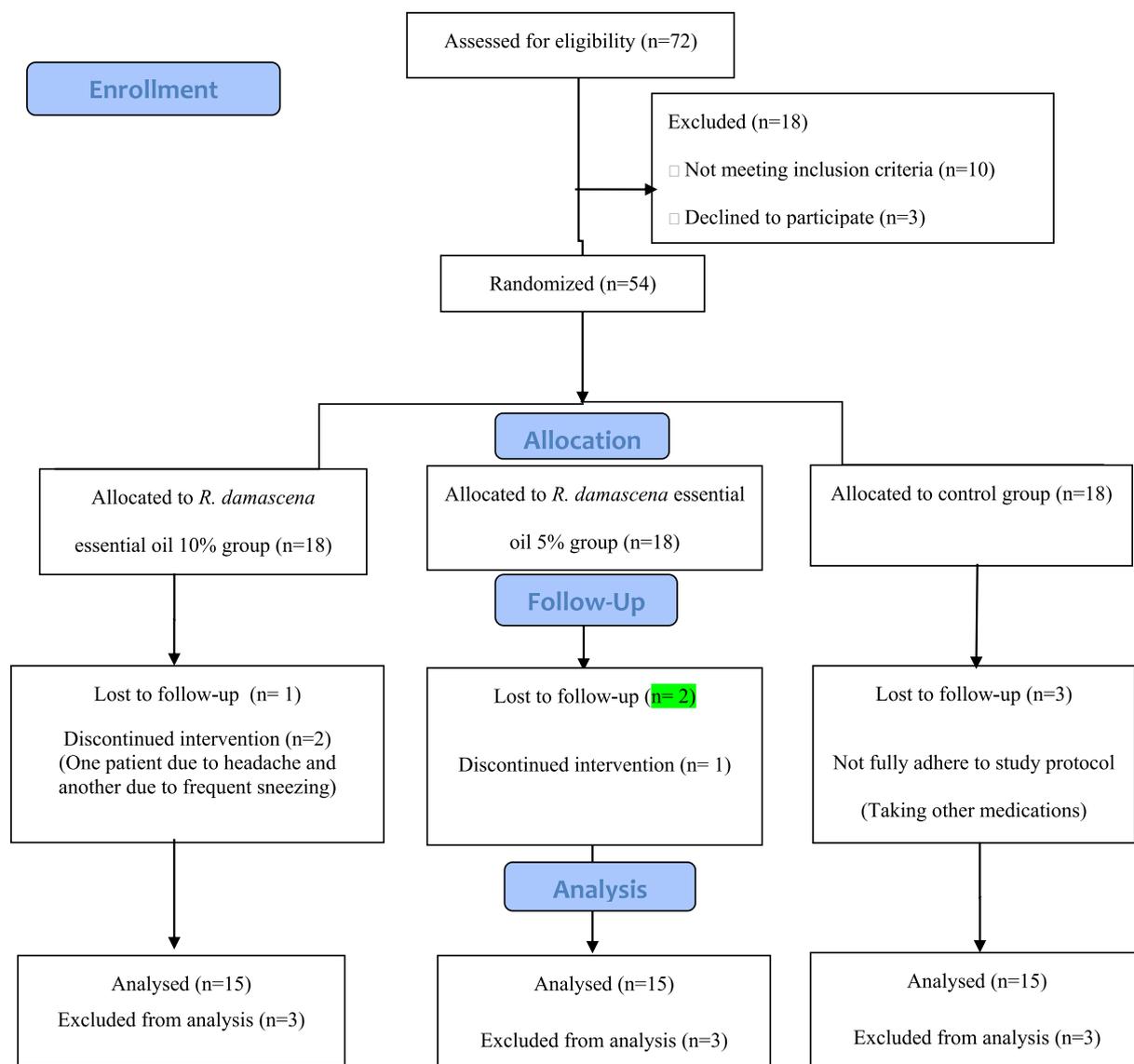
Fig. 1. CONSORT flow diagram of the study inclusion, allocation and follow-up.

4. Discussion

In this study, the effect of aromatherapy with two different concentrations of *R. damascena* essential oil on the quality of sleep in cancer patients was investigated and the results showed that the patients' sleep quality was significantly improved in two aromatherapy groups in comparison to the control group. In the two experimental groups, sleep latency was significantly lower than the control group; also, the duration of night sleep in the two experimental groups was significantly higher than the control group. The results showed that the mean score of the total Pittsburgh Index was the same for both concentrations (P-value = 0.001), suggesting that it would be cost-effective to use 5% essential oil as complementary medication for sleep disorders, but the assessment of each parameter showed that the

concentration of 10% was more effective in sleep latency, mean score of sleep quality, and mean duration of night sleep compared to the 5% concentration.

The findings of this study are in line with the results of Hajibagheri et al. [27]. They investigated the effect of *R. damascena* aromatherapy on the quality of sleep among the patients hospitalized in CCU. They found that *R. damascena* aromatherapy reduces the sleep latency and sleep disturbances and improves the duration and subjective quality of sleep. Although there were few studies similar to our study, some studies have better interpret our study results. For example, Heydari et al. investigated the efficacy of aromatherapy with essential oils of *R. damascena* for the management of premenstrual syndrome. In their triple blind randomized clinical trial, *R. damascena* improved the multiple symptoms of premenstrual syndrome [28]. Another study assessed the

Table 1
Demographic data of the patients in the three groups of the study.

Demographic data	Essential oil 5% (N* = 15)	Essential oil 10% (N = 15)	Control (N = 15)	*P* value
Age (years), Mean(± SD**)	47.60 ± 10.76	50.00 ± 13.94	50.20 ± 18.54	0.693
Male/female (%)	3/12(20/80%)	6/9(40/60%)	8/7(53/47%)	0.166

*N: Number **SD: Standard Deviation.

Table 2
The Pittsburgh Index scores before and after the intervention in the three groups of the study.

Outcome masseurs	Study groups	Before	After	P-value
Total Pittsburgh Index score	Essential oil 5%	13.46 ± 2.79	8.40 ± 3.58	0.001
	Essential oil 10%	13.80 ± 2.45	7.40 ± 3.66	0.001
	Control	14.33 ± 2.35	13.66 ± 2.02	0.041
	P-value	0.688	0.000	
Sleep latency(minute)	essential oil 5%	101.07 ± 77.14	26.42 ± 28.85	0.003
	essential oil 10%	114.00 ± 54.32	28.50 ± 29.48	0.001
	Control	76.66 ± 61.72	66.66 ± 57.55	0.593
	P-value	0.114	0.007	
Mean score of sleep quality	essential oil 5%	3.20 ± 0.67	2.06 ± 0.88	0.004
	essential oil 10%	3.46 ± 0.51	2.06 ± 0.79	0.001
	Control	3.20 ± 0.67	2.93 ± 0.88	0.206
	P-value	0.254	0.015	
Mean duration of night sleep	essential oil 5%	3.21 ± 1.41	4.68 ± 2.13	0.007
	essential oil 10%	3.60 ± 1.25	5.40 ± 1.62	0.003
	Control	3.90 ± 1.47	4.26 ± 1.46	0.180
	P-value	0.415	0.224	

effects of aromatherapy with *R. damascena* on pain and anxiety in the first stage of labor among nulliparous women and showed that aromatherapy with *R. damascena* reduced the severity of pain and anxiety in the first stage of labor [29]. In these two studies, fatigue, pain and anxiety of patients with aromatherapy with *R. damascena* improved. It is known that fatigue, anxiety and pain can cause sleep disorders or reduce the sleep quality, especially in cancer patients might be reduction of pain, anxiety and fatigue in cancer patients.

Studies show that aromatic molecules cause a number of neurotransmitters such as dopamine and serotonin to be released in the central nervous system by stimulating the olfactory system and affecting the limbic system [32]. Moreover, preclinical and clinical studies suggest that the therapeutic effect of nose-to-brain drug delivery in sleep disorders has promising outcomes [33–35]. Considering the existing evidence, we can infer that aromatherapy could affect the sleep quality.

Other experimental and clinical evidence suggests that *R. damascena* essential oil has anti-anxiety properties [21,36]. Studies also show that sleep quality would be improved by controlling anxiety [37]. It seems that after inhalation of *R. damascena* essential oil and stimulation of the brain system by releasing neurotransmitters such as dopamine and serotonin, cancer patients have less stress; consequently, they sleep better. Our study results confirm those of the previous studies.

The valuable point of this study is that our intervention was non-oral, which is particularly important in cancer patients undergoing chemotherapy, because one of the important precautions in this period is drug interactions with chemotherapy drugs. Also, patients who are under chemotherapy often have nausea and vomiting; hence, non-oral medication can be suitable.

This study had several potential limitations. Lack of objective outcome masseurs for evaluation of sleep quality was one of its main limitations. In this study, we used a subjective questionnaire for assessing the quality of sleep; although its validity and reliability for assessing the quality of sleep had been confirmed before, it was less accurate than other methods such as monitoring the brain waves during sleep. The small sample size and short duration of the trial were other limitations of the study.

5. Conclusion

The results of this study showed that the cancer patients' sleep quality was significantly improved in two aromatherapy groups with two different concentrations of *R. damascena* essential oil in comparison to the control group. Therefore, it seems that aromatherapy with *R. damascena* essential oil could be considered as a suitable complementary therapy for improvement of sleep quality of the cancer patients. However, well-designed, randomized controlled trials with long-time follow up are recommended to be conducted.

References

[1] J.A. Roscoe, M.E. Kaufman, S.E. Matteson-Rusby, O.G. Palesh, J.L. Ryan, S. Kohli, M.L. Perlis, G.R. Morrow, Cancer-related fatigue and sleep disorders, Oncol. 12 (Supplement 1) (2007) 35–42.

[2] V.-E. Gordana, Š. Zoran, J.-S. Jasmina, Benzodiazepine poisoning in elderly, Vojnosanit. Pregl. 73 (3) (2016) 234–238.

[3] S. Mosavat, M. Heyadri, M. Hashempur, S. Dehghani, Use of complementary and alternative medicine among pediatric patients with hepatic and gastrointestinal diseases, East. Mediterr. Health J. 24 (10) (2018) 1018–1025.

[4] A. Shakeri, M. Hashempur, M. Mojibian, F. Aliasl, S. Bioos, F. Nejatbakhsh, A comparative study of ranitidine and quince (Cydonia oblonga mill) sauce on gastroesophageal reflux disease (GERD) in pregnancy: a randomised, open-label, active-controlled clinical trial, J. Obstet. Gynaecol. (2018) 1–7.

[5] M. Jabbari, B. Daneshfard, M. Emtiazy, A. Khiveh, M.H. Hashempur, Biological effects and clinical applications of Dwarf Elder (Sambucus ebulus L): a review, Journal of evidence-based complementary & alternative medicine 22 (4) (2017) 996–1001.

[6] G. Heydarirad, S.M.H. Sadeghi, S.M.H. Khameneh, M. Khodadoost, M. Kamalinejad, S. Jafari, L. Gachkar, Effects of natural substances on healing of long bone fractures: a narrative review of traditional Persian medicine, Galen Medical Journal 5 (4) (2016) 165–172.

[7] L. Marchand, Integrative and complementary therapies for patients with advanced cancer, Ann. Palliat. Med. 3 (3) (2014) 160–171.

[8] G. Heydarirad, H. Rezaeizadeh, R. Choopani, S.H. Mosavat, A. Ameri, Efficacy of a traditional Persian medicine preparation for radiation-induced xerostomia: a randomized, open-label, active-controlled trial, Journal of integrative medicine 15 (3) (2017) 201–208.

[9] P.M. Herman, B.M. Craig, O. Caspi, Is complementary and alternative medicine (CAM) cost-effective? A systematic review, BMC Complement Altern. Med. 5 (1) (2005) 11.

[10] M.J. Qasemzadeh, H. Sharifi, M. Hamedanian, M. Gharehbeglou, M. Heydari, M. Sardari, M. Akhlaghdoust, M.B. Minae, The effect of Viola odorata flower syrup on the cough of children with asthma: a double-blind, randomized controlled trial, Journal of evidence-based complementary & alternative medicine 20 (4) (2015) 287–291.

[11] M.S. Lee, J. Choi, P. Posadzki, E. Ernst, Aromatherapy for health care: an overview of systematic reviews, Maturitas 71 (3) (2012) 257–260.

[12] W.-W. Tao, H. Jiang, X.-M. Tao, P. Jiang, L.-Y. Sha, X.-C. Sun, Effects of acupuncture, tuina, tai chi, qigong, and traditional Chinese medicine five-element music therapy on symptom management and quality of life for cancer patients: a meta-analysis, J. Pain Symptom Manag. 51 (4) (2016) 728–747.

[13] Ö. Ülger, N.V. Yağlı, Effects of yoga on the quality of life in cancer patients, Complement. Ther. Clin. Pract. 16 (2) (2010) 60–63.

[14] A.S. Keyhanmehr, S. Kolouri, G. Heydarirad, B. Mofid, S.H. Mosavat, Aromatherapy for the Management of Cancer Complications: A Narrative Review, Complementary Therapies in Clinical Practice, (2018).

[15] A.S. Keyhanmehr, M. Movahhed, S. Sahranavard, S. Hamdieh, S. Afsharpaiman, L. Gachkar, H. Nikfarjad, Which aroma in Iranian traditional medicine is effective on sleep disorders? Galen Medical Journal 6 (1) (2017) 3–11.

[16] E. Fradelos, A. Komini, The use of essential oils as a complementary treatment for anxiety, J AJN 4 (1) (2015) 1–5.

[17] A.S. Lillehei, L.L. Halcon, A systematic review of the effect of inhaled essential oils on sleep, J. Alternative Compl. Med. 20 (6) (2014) 441–451.

[18] E. Hwang, S. Shin, The effects of aromatherapy on sleep improvement: a systematic literature review and meta-analysis, J. Alternative Compl. Med. 21 (2) (2015) 61–68.

[19] M.-Y. Cho, E.S. Min, M.-H. Hur, M.S. Lee, 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).

[20] M. Niazi, M.H. Hashempur, M. Taghizadeh, M. Heydari, A. Shariat, Efficacy of topical Rose (Rosa damascena Mill.) oil for migraine headache: a randomized double-blinded placebo-controlled cross-over trial, Complement. Ther. Med. 34 (2017) 35–41.

[21] M.H. Boskabady, M.N. Shafei, Z. Saberi, S. Amini, Pharmacological effects of Rosa damascena, Iranian Journal of Basic Medical Sciences 14 (4) (2011) 295.

[22] A. Keyhanmehr, M. Movahhed, S. Sahranavard, L. Gachkar, M. Hamdieh, S. Afsharpaiman, H. Nikfarjad, The effect of aromatherapy with Rosa damascena essential oil on sleep quality in children, Research Journal of Pharmacognosy 5 (1) (2018) 41–46.

[23] M.H. Hashempur, M.M. Hashempour, S.H. Mosavat, M. Heydari, Rhazes—his life and contributions to the field of dermatology, JAMA dermatology 153 (1) (2017) 70-70.

[24] A. Khiveh, M.H. Hashempur, M. Shakiba, M.H. Lotfi, A. Shakeri, S. Kazemeini, Z. Mousavi, M. Jabbari, M. Kamalinejad, M. Emtiazy, Effects of rhubarb (Rheum ribes L.) syrup on dysenteric diarrhea in children: a randomized, double-blind, placebo-controlled trial, Journal of integrative medicine 15 (5) (2017) 365–372.

[25] R. Akrami, M.H. Hashempur, A. Tavakoli, M. Nimrouzi, M. Sayadi, M. Roodaki, J. Roozbeh, P. Faridi, Effects of Fumaria parviflora L on uremic pruritus in hemodialysis patients: a randomized, double-blind, placebo-controlled trial, Jundishapur J. Nat. Pharm. Prod. 12 (3) (2017) e39744 Supp).

[26] S.L. Beck, A.L. Schwartz, G. Towsley, W. Dudley, A. Barsevick, Psychometric evaluation of the Pittsburgh sleep quality Index in cancer patients, J. Pain Symptom Manag. 27 (2) (2004) 140–148.

[27] A. Hajibagheri, A. Babaii, M. Adib-Hajbaghery, Effect of Rosa damascene aromatherapy on sleep quality in cardiac patients: a randomized controlled trial, Complement. Ther. Clin. Pract. 20 (3) (2014) 159–163.

[28] N. Heydari, M. Abootalebi, N. Jamalimoghadam, M. Kasraeian, M. Emamghoreishi, M. Akbarzaded, Evaluation of aromatherapy with essential oils of Rosa damascena for the management of premenstrual syndrome, Int. J. Gynecol. Obstet. 142 (2) (2018) 156–161.

[29] S. Hamdamian, S. Nazarpour, M. Simbar, S. Hajian, F. Mojab, A. Talebi, Effects of aromatherapy with Rosa damascena on nulliparous women's pain and anxiety of labor during first stage of labor, Journal of integrative medicine 16 (2) (2018) 120–125.

[32] X. Nan Lv, Z. Jun Liu, H. Jing Zhang, C.M. Tzeng, Aromatherapy and the central nerve system (CNS): therapeutic mechanism and its associated genes, Curr. Drug Targets 14 (8) (2013) 872–879.

[33] A. Pires, A. Fortuna, G. Alves, A. Falcão, Intranasal Drug Delivery: How, Why and what for? (2009).

[34] Z. Abolhasanzadeh, H. Ashrafi, P. Badr, A. Azadi, Traditional neurotherapeutics approach intended for direct nose to brain delivery, J. Ethnopharmacol. 209 (2017) 116–123.

[35] Z. Feyzabadi, F. Jafari, S.H. Kamali, H. Ashayeri, S.B. Aval, M.M. Esfahani, O. Sadeghpour, Efficacy of Viola odorata in treatment of chronic insomnia, Iran. Red Crescent Med. J. 16 (12) (2014).

[36] B.F. Bradley, N. Starkey, S. Brown, R. Lea, The effects of prolonged rose odor inhalation in two animal models of anxiety, Physiol. Behav. 92 (5) (2007) 931–938.

[37] C.M. Morin, Measuring outcomes in randomized clinical trials of insomnia treatments, Sleep Med. Rev. 7 (3) (2003) 263–279.