Herbal Medicines Journal **2020; 5(3):119-26**
DOI: 10.22087/herb%20med%20j.v5i3.822 **ISSN:** 2538-2144

Clinical Trails

Complementary Effects of *Mentha piperita* (Peppermint) and *Rosa damascene* Extract (Rose oil) on SpO_2 in Patients with COVID-19: A Randomized Clinical Trial

Davood Ommi[1], Nima Saeedi[1], Nastaran Hajizadeh[2], Gholamreza Mohseni[1], Houman Teymourian[1]*

[1]Department of Anesthesiology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 12.08.2020; Accepted: 26.01.2021

Abstract

Background and Aim: In light of the high prevalence of COVID-19 and the need for ventilation support, various methods have been recommended to decrease the need for mechanical ventilation support. In the present study, we made an attempt to compare the effects of rose oil and peppermint extract nebulizer on SpO_2 (peripheral oxygen saturation) in COVID-19's patients.

Materials and Methods: This study was conducted on 60 patients with COVID-19 under a standard treatment protocol at the Northeast Corona Center of Tehran. The patients were divided into three groups, i.e. peppermint (n:20), rose oil (n:20) and the control (n:20). The peppermint group received peppermint oil nebulizer twice a day (12 drops in 30cc sterile water for each time), the rose oil group received rose oil nebulizer twice a day (12 drops in 30cc sterile water for each time) and the control group received sterile water with nebulizer (30cc sterile water). SpO_2 without extra O_2 support was recorded before the start of the nebulizing every day up to 3 days.

Results: The results revealed that the mean SpO_2 significantly increases over time in all the three groups (P-value<0.001). The mean SpO_2 was 84.97 ± 0.5 before the treatment, but it was increased to 86.83 ± 0.4 , 88.32 ± 0.4, and 89.93 ± 0.4 at the first, second and third days of the treatment respectively. The daily increase was statistically significant (P-value<0.001). The results showed that mean SpO_2 of the peppermint group was significantly more than the control group at the third day of the treatment. The difference in saturation was 3.25% and the p-value was 0.004. Hence, the need for mechanical ventilation reduced and the patients' satisfaction increased.

Conclusion: The patients experiencing decreases in SpO_2 who were treated with peppermint extract showed better results than those treated with placebo at the third day.

Keywords: COVID-19, Mentha piperita, Nebulizer, Rosa damascene

***Corresponding Author:** Houman Teymourian, Associate professor of Anesthesiology, Neurofunctional Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel/Fax: +98-22741174. E-mail: houman72625@yahoo.com.
Please cite this article as: Ommi D, Saeedi N, Hajizadeh N, Mohseni Gh, Teymourian H. Complementary Effects of *Mentha piperita* (Peppermint) and *Rosa damascene* Extract (Rose oil) on SpO_2 in Patients with COVID-19: A Randomized Clinical Trial. Herb. Med. J. 2020; 5(3):119-26.

Introduction

Due to the high rate of pulmonary involvement in patients with COVID-19, choosing the appropriate treatment method will have a great impact on patients' pulmonary condition affected by COVID-19 and subsequently reduce the need for respiratory support. Decreased blood oxygen saturation is common in patients with COVID-19 that might be mild to moderate, and sometimes leads to oxygen therapy or NIV (Non-Invasive Ventilation) and even intubation and mechanical ventilation. Various therapies are used to improve the patients' respiratory conditions. One of these methods is the use of nebulized medications such as salbutamol.

Over 25 essential oils have been officially mentioned in the European Pharmacopoeia, and some of them are used for the treatment of respiratory tract diseases (e.g. anise oil, bitter fennel fruit, eucalyptus, peppermint, tea tree and thyme) (1).

The probabilistic mechanism of action of respiratory administration of aromatherapy involves the absorption of drug particles by the nasal mucosa and its transformation into a chemical signal. These signals send to the olfactory bulb and then to amygdala and limbic system, interacting with the neuropsychological framework to effect the respiratory system or other organs (2). The rose oil (Rosa damascena extract) contains flavonoids, carboxylic acids terpene, tannins, myrcene and vitamin C and also has antioxidative effect (3-5). Rose oil traditionally has been used for chronic cough and also as an anti-inflammatory agent. Moreover, it is used as a remedy for digestive problems (6).

Furthermore, peppermint (Mentha piperita) extract has antimicrobial effects on the respiratory system and inhibits microbial activity (7). It has several properties such as anti-nausea, antioxidant and antispasmodic effects on the gastrointestinal tract (8-10). Due to the need for oxygen therapy in patients with COVID-19, the use of nebulizers as an adjuvant therapy in these patients can contribute to the improvement of their respiratory conditions. Many herbs such as those mentioned above can be used in traditional–Islamic medicine. Therefore, we decided to compose two of the most used herbs in IRAN.

Materials and Methods

Study Design: This randomized clinical trial was conducted at Shahid Beheshti University of Medical Sciences based on the protocol proposed by at the Northeast Corona Center of Tehran. (Ethic code: IR.SBMU.RETECH.REC.1399.353)

(Iranian Clinical Trial Code: IRCT20190131042569N5)

Sample Size: All the patients signed an informed consent form before enrolment in the study. The required sample size (11) to achieve the power 80% and significance level 5% for multiple comparison of $k = 3$ treatment groups was 20 patients for each group (60 patients in total), using the following formula:

$$n = \frac{\lambda}{\frac{1}{\sigma^2}\sum_{i=1}^{k}(\mu_i - \mathrm{M})}.$$

which $\lambda = 9.64$ is the non-centrality parameter for comparing 3 groups, μ_i shows the mean of each group, and $\mathrm{M} = \frac{1}{k}\sum_{i=1}^{k}\mu_i$.

Subjects: The participants who registered for the study were patients with evidence of COVID-19 in chest CT scan and in an age group between 30-60 years old. They did not have any history of asthma, COPD or allergy. They were divided into three groups by random number table; i.e. peppermint extract ***(P)*** (n:20), rose oil ***(R)*** (n:20) and the control group ***(C)*** (n:20). Exclusion criteria for the study were: (1) the need for intubation, (2) allergic reaction to rose oil or peppermint during the study.

Intervention: All the patients received Azithromycin 250 mg BD, Hydroxychloroquine 200 mg BD and Naproxen 250 mg BD as their standard treatment and 6 L/min O_2 support with face mask and reservoir bag during hospitalization. The first evaluation of SpO_2 (Peripheral oxygen saturation) was done prior to starting complementary and standard medical treatments. Standard monitoring was applied and SpO_2 without oxygen supplement was recorded.

Peppermint Group: From the beginning of the treatment, the patients received nebulizing of peppermint oil from Noshad brand from Ganjineh Osareh Tabiat Ph CO., Isfahan, Iran (15 drops in 30 cc

of distilled water), daily and each time for 2 hours during 3 days. (http://www.noshadco.co/Product/ProductDetails/21)
Rose Oil Group: From the beginning of the treatment, the patients received nebulizing of rose oil from Barij Essence brand from Darou Gostar Barij Essence CO., Mashhad Ardehal – Kashan -Iran (15 drops in 30 cc of distilled water), daily and each time for 2 hours during 3 days. (http://barijessence.com/product/rose-drop/)
The Control Group: From the beginning of the treatment, the patients received nebulizing of distilled water (30 cc) daily and each time for 2 hours during 3 days.
All of these medications (rose oil and peppermint oil) were supplied by our team.
At the first, second and third days of nebulizing, the patients' SpO2 was measured without extra oxygen support (after 3 minutes breathing in room air) and recorded. If a patient was not able to tolerate breathing without oxygen, oxygen supplement was immediately used. During the study, one patient in the peppermint group, one case in the rose oil group, and two cases in the control group needed intubation (mechanical ventilation). Therefore, they were excluded and replaced with other patients. All the participants and the physicians who filled the questionnaire were unaware of patients' groups.

Statistical Analysis: The data was entered into Microsoft Excel and analyzed using student's t-test, chi-square test and ANOVA. A p-value of < 0.05 was considered statistically significant.

Results and Discussion

Table-1 indicates the demographic features in the 3 groups. It shows no significant difference between the mean age and values of vital signs, including mean heart rate, mean systolic and diastolic blood pressure in the rose oil, peppermint, and control groups.
The results of repeated measure test determined that the mean percentage of saturation significantly increases over time in each of the three groups (P-value<0.001). The estimated mean percentage of saturation was 84.97 ± 0.5 before the treatment. However, it was increased to 86.83 ± 0.4, 88.32 ± 0.4,

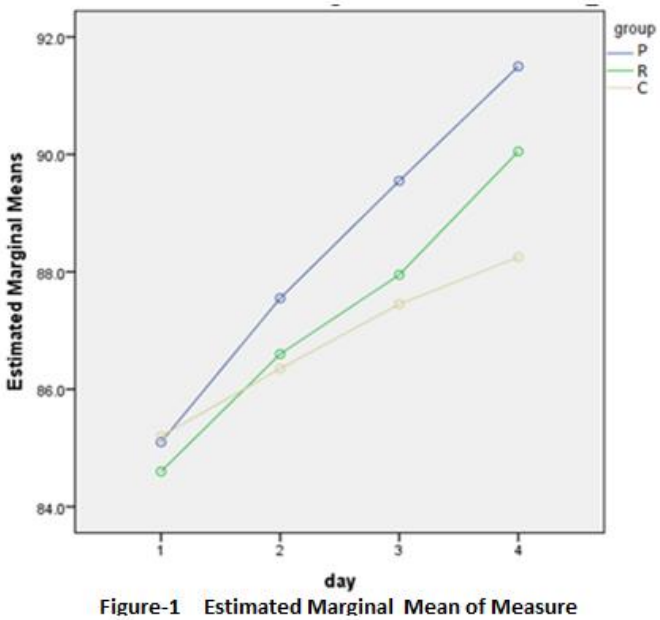

Figure-1 Estimated Marginal Mean of Measure

Figure 1. Spo2 percentage in three groups shows significant increase in P group followed by R group. P; Peppermint, R; Rose oil, C; control

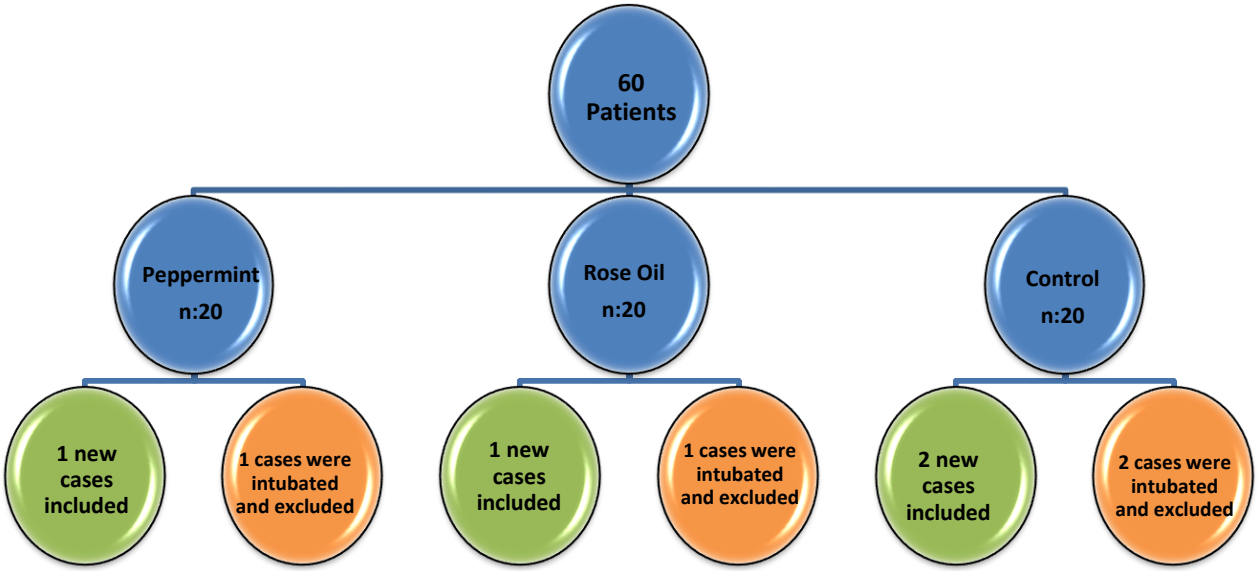

Figure 2. Descriptive statistics

and 89.93±0.4 at the first, second and third days of the treatment respectively. Day to day increases were statistically significant (P-value< 0.001) (Table-2) (Figure-1). The results of one-way ANOVA test showed that the mean percentage of saturation of the peppermint group was significantly higher than the control group at the third day of the treatment. The difference in saturation was 3.25% and the p-value was 0.004 (Table-2).

COVID-19, which is caused by SARS-COV2, is the most important health problem these days and has an extremely adverse effect on global public health (12). The nature of this disease is mainly pulmonary involvement that in some patients requires oxygen therapy , NIV or even intubation and mechanical ventilation (13).

Many medicines and treatment methods have been tried to improve respiratory conditions of infected patiens. Numerous remedies have long been used to improve lung conditions, including intravenous, inhaled, and traditional therapies. One of these traditional treatments used for respiratory infections is the use of herbal and essential oil extracts as nebulizing agents. A mixture of rose (*Rosa damascena*) oil and water has been used in traditional medicine since the seventh century. This mixture has several properties that have been used to treat chronic cough, certain allergies, and migraines. Moreover, it has been used to reduce inflammation, heal wounds, cure digestive problems and reduce tention stress (14-16). Rose water has antibacterial, hypnotic and sedative properties. It also has anti-HIV effects (17). The effect of rose oil on cough frequency following stimulant agents in animals was investigated in a study. The results indicate a decrease in the number of coughs following rose oil use (18). Rose oil has bronchodilatory and antitussive effects (19). The studies showed that rose oil had a potent relaxant effect that was comparable to theophylline (18). Its exact mechanism of antitussive effect is not well understood yet, but it might be due to its probabilistic tachykinin inhibitory effect. In a study conducted by Mohamed Shohayeb on the antimicrobial effect of rose oil on three Gram-positive bacteria and seven

Table 1: Demographic features; Result showed no significant difference between groups.

		Rose oil	Peppermint	Control
Age (y, Mean ± SD)		52.0±8.42	48.92±9.05	50.12±8.37
Gender	Female	5	6	6
	Male	15	14	14
Heart Rate		91.5±8.13	90.5±6.61	90.4±7.64
Systolic Blood Pressure (mmHg, Mean ± SD)		101.2±13.5	100.9±10.11	101.5±11.18
Diastolic Blood Pressure (mmHg, Mean ± SD)		66.0±7.20	69.1±4.60	65.8±7.21

Table 2: Descriptive statistics ; SpO_2 measures in three consecutive days; Although SpO_2 increases statically significant over time in each three groups, mean percentage of saturation of the *P* group is significantly more than other two groups.

Day	Group	Mean percentage of saturation	Std. Deviation
day0	***(P)***	85.10	3.85
	(R)	84.60	4.17
	(C)	85.20	3.66
	Total	84.97	3.84
day1	***(P)***	87.55	3.09
	(R)	86.60	3.66
	(C)	86.35	3.30
	Total	86.83	3.34
day2	***(P)***	89.55	2.14
	(R)	87.95	3.39
	(C)	87.45	3.39
	Total	88.32	3.12
day3	***(P)***	91.50	2.48
	(R)	90.05	3.20
	(C)	88.25	3.38
	Total	89.93	3.28

Gram-negative bacteria, one acid-fast bacterium showed that R. damascena essential oil and different extracts of petals had broad spectrum antibacterial activity (20). Peppermint extract also has antimicrobial effects on the respiratory system and inhibits microbial activity (7). Peppermint extract has several properties such as anti-nausea, antioxidant and antispasmodic effects on the gastrointestinal tract (8, 9).

WU QF *et al*. showed that Mosla dianthera (an essential oil) had remarkable impacts on lung viral titers reduction, inhibiting pneumonia, IFN-γ and IL-4

serum level reduction. Furthermore, it had antioxidant effect on the lung tissue of mice with influenza (21). Salim MA Bastaki *et al*. conducted a study on rats in which colitis was induced using acetic acid. They showed that increased calprotectin levels were significantly reduced in the menthol group, indicating that menthol suppresses inflammatory processes in colonic tissues. Furthermore, calprotectin, and production of pro-inflammatory cytokines such as IL-1, IL-6, IL-23, and TNF-α in inflamed colonic tissue was also significantly reduced in the menthol group (22). In earlier studies, menthol has been shown to decrease inflammatory cytokine levels in the gastric tissue and monocytes (23).

Li Y *et al.* indicated that ethanol extract of Mentha piperita contained high levels of phenolic acid and flavonoids. Moreover, they reportyed that it could have antiviral activity against respiratory syncytial virus with a high selectivity index, and significantly reduce TNF-α, NO, IL-6, and PGE2 production in lipopolysaccharide-stimulated RAW 264.7 cells. Also, Mentha piperita showed potential free-radical scavenging activities (24). In a study conducted by Hassan Rakhshandeh on animals, the effects of theophylline and rose oil extract on smooth muscles were investigated. The results showed that the effect of rose oil extract on smooth muscle relaxation of the airways was higher than theophylline (25). The results of the study by Seyhan Ulusoy *et al*. showed that rose oil extract could have strong antimicrobial effects (26). In another study conducted by Xin Liu *et al*., the anti-tumor and antioxidant effects of peppermint extract in the laboratory on tumor and cancer cells were confirmed (27). Maryam Marofi *et al*. carried out a research on the effect of aroma therapy with Rosa damascena on postoperative pain intensity in children. The results of their study showed that the pain score was remarlably decreased in the aromatherapy group with *R. damascena* Mill compared to the control group (28). In this study (ethical Cod: R.SBMU.RETECH.REC.1399.346 and IRCT: 20190131042569N4), we compared the complementary effects of nebulizing peppermint extract and rose oil on SpO_2 in patients with COVID-19. The patients with evidence of COVID-19 in their chest CT Scan who were admitted in the ward (not in ICU) and were not candidates for receiving Remdisivir or Kaletra were selected. They received O_2 supplement and medical treatment as other patients in this hospital and we added these inhaled suplements to improve their respiratory condition. First, their SpO_2 without O_2 supplements were recorded and then every day up to 3 days of treatment with nebulizing agents. Initially, the mean patients' SpO_2 was 84.6% in the rose oil group, 85.1% in Peppermint group and 85.2% in control group. first day of treatment, the mean SpO_2 was 86.6% in the rose oil group, 87.55% in the peppermint group, and 86.35% in the control group, and showed that the patients in three groups experienced increasing SpO_2 but the differences between the groups were not significant. On the second day of treatment, the mean SpO_2 was 87.95% in the rose oil group, 89.55% in the peppermint group, and 87.45% in the control group, and showed that the patients in the three groups experienced SpO_2 increase but the differences between the groups were not significant. On the third day, the mean SpO_2 was 90.05% in the rose oil group, 91.5% in the peppermint group and 88.25% in the control group, and shows that the patients in the peppermint group experienced more SpO_2 increase than the control group and its difference is significant but the difference between the rose oil and the control group was not significant (Table-2). Our data showed that the patients in every group experienced more significant improvements day by day in SpO_2.

The results of repeated measure test determined that the mean percentage of saturation was increased significantly over time in each group (P-value<0.001). The estimated mean percentage of saturation was 84.97 ± 0.5 before the treatment, but it was increased to 86.83 ± 0.4, 88.32 ± 0.4, and 89.93 ± 0.4 at the first, second and third days of the treatment respectively. Day to day increases were statistically significant (P-value<0.001). The results of one-way MANOVA test showed that the mean percentage of saturation of the peppermint group is significantly more than the control group at the third day of the treatment. The difference in saturation was 3.25% (p-value 0.004). It means that the need for mechanical ventilation is reduced and patients' satisfaction is affected (Table-2). According to previous studies, peppermint has potential free-radical scavenging activities and

suppresses inflammatory process and also decreases inflammatory cytokines such as IL-1, IL-6, IL-23, and TNF-α (22-24). Therefore, this SpO_2 improvement can be due to peppermint's anti-inflammatory effects.

Conclusion

According to the data obtained from this study, coplementary nebulizing peppermint oil seems to have a statiscally significant positive effect on SpO_2 in COVID-19 patients under standard medical treatment. It is recommended in patients with COVID-19. The authors do not recommand using this method solely instead of standard treatment provided by WHO and(or) local health policies. Further studies on the efficacy of nebulizing peppermint oil on SpO_2 in these patients (larger sample size and combining with other medications) are required to minimize the possibility of the occurrence of decreased SpO_2. Moreover, the and need for ventilation support is also evident.

Acknowledgment

The authors would like to thank Neurofunctional Research Center, dedicated personnel of corona ward, Shohada Tajrish Hospital, Tehran, and all the people who participated in this research.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1.Štefanidesová K, Špitalská E, Csicsay F, Friedländerová V, Šáner A, Škultéty Ľ. Evaluation of the possible use of genus Mentha derived essential oils in the prevention of SENLAT syndrome caused by Rickettsia slovaca. Journal of ethnopharmacology. 2019;232:55-61.
2.de Jong M, Lucas C, Bredero H, van Adrichem L, Tibboel D, van Dijk M. Does postoperative 'M'technique® massage with or without mandarin oil reduce infants' distress after major craniofacial surgery? Journal of advanced nursing. 2012;68(8):1748-57.
3.Libster M. Delmar's integrative herb guide for nurses: Delmar/Thomson Learning; 2002.
4.Schieber A, Mihalev K, Berardini N, Mollov P, Carle R. Flavonol glycosides from distilled petals of Rosa damascena Mill. Zeitschrift für Naturforschung C. 2005;60(5-6):379-84.
5.Yasa N, Masoumi F, ROUHANI RS, HAJI AA. Chemical composition and antioxidant activity of the extract and essential oil of Rosa damascena from Iran, population of Guilan. 2009.
6.Hajhashemi V, Ghannadi A, Hajiloo M. Analgesic and anti-inflammatory effects of Rosa damascena hydroalcoholic extract and its essential oil in animal models. Iranian journal of pharmaceutical research: IJPR. 2010;9(2):163.
7.Edris AE. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: a review. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2007;21(4):308-23.
8.Tayarani-Najaran Z, Talasaz-Firoozi E, Nasiri R, Jalali N, Hassanzadeh M. Antiemetic activity of volatile oil from Mentha spicata and Mentha× piperita in chemotherapy-induced nausea and vomiting. ecancermedicalscience. 2013;7.
9.Asao T, Mochiki E, Suzuki H, Nakamura J-i, Hirayama I, Morinaga N, et al. An easy method for the intraluminal administration of peppermint oil before colonoscopy and its effectiveness in reducing colonic spasm. Gastrointestinal endoscopy. 2001;53(2):172-7.
10. Chrubasik S. ESCOP Monographs. The Scientific Foundation for Herbal Medicinal Products. Supplement 2009; Thieme Publisher: Stuttgart, New York; ESCOP 2009, ISBN 978-1-901964-08-0 (ECOP), ISBN 978-3-13-149981-3 (GTV),(Postage and packing per copy to the UK or Europe). Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2010;24(3):474-.
11. Chow S-C, Wang H, Shao J. Sample size calculations in clinical research: CRC press; 2007.
12. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity. 2020:102433.
13. Zhang J, Zhou L, Yang Y, Peng W, Wang W, Chen X. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. The Lancet Respiratory Medicine. 2020;8(3):e11-e2.
14. Sharafkhandy A. Ave-Sina. Law in Medicine. Interpreter. Ministry of Guidance Publication, Teheran. 1990.
15. Momeni T, Shahrokhi N. Essential oils and their therapeutic actions. Tehran: Tehran. 1991.
16. Zargari A. Iranian medicinal plants. Tehran: Tehran University Publications. 1997.
17. Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of Rosa damascena. Iranian journal of basic medical sciences. 2011;14(4):295.
18. Shafei MN, Rakhshandah H, Boskabady MH. Antitussive effect of Rosa damascena in guinea pigs. Iranian Journal of Pharmaceutical Research. 2010:231-4.
19. Advenier C, Lagente V, Boichot E. The role of tachykinin receptor antagonists in the prevention of bronchial hyperresponsiveness, airway inflammation and cough. European Respiratory Journal. 1997;10(8):1892-906.
20. Shohayeb M, Abdel-Hameed E-SS, Bazaid SA, Maghrabi I. Antibacterial and antifungal activity of Rosa damascena MILL. essential oil, different extracts of rose petals. Global Journal of Pharmacology. 2014;8(1):1-7.
21. Wu Q-f, Wang W, Dai X-y, Wang Z-y, Shen Z-h, Ying H-z, et al. Chemical compositions and anti-influenza activities of essential oils from Mosla dianthera. Journal of ethnopharmacology. 2012;139(2):668-71.
22. Bastaki SM, Adeghate E, Amir N, Ojha S, Oz M. Menthol inhibits oxidative stress and inflammation in acetic acid-induced colitis in rat colonic mucosa. American journal of translational research. 2018;10(12):4210.
23. Rozza AL, de Faria FM, Brito ARS, Pellizzon CH. The gastroprotective effect of menthol: involvement of anti-apoptotic, antioxidant and anti-inflammatory activities. PloS one. 2014;9(1).

24. Li Y, Liu Y, Ma A, Bao Y, Wang M, Sun Z. In vitro antiviral, anti-inflammatory, and antioxidant activities of the ethanol extract of Mentha piperita L. Food science and biotechnology. 2017;26(6):1675-83.
25. Rakhshandah H, Boskabadi M, MOUSAVI Z, GHOLAMI M, Saberi Z. The Differences in the relaxant effects of different fractions of Rosa damascena on guinea pig tracheal smooth muscle. 2010.
26. Ulusoy S, Boşgelmez-Tınaz G, Seçilmiş-Canbay H. Tocopherol, carotene, phenolic contents and antibacterial properties of rose essential oil, hydrosol and absolute. Current microbiology. 2009;59(5):554.
27. Liu X, Sun Z-L, Jia A-R, Shi Y-P, Li R-H, Yang P-M. Extraction, preliminary characterization and evaluation of in vitro antitumor and antioxidant activities of polysaccharides from Mentha piperita. International journal of molecular sciences. 2014;15(9):16302-19.
28. Marofi M, Sirousfard M, Moeini M, Ghanadi A. Evaluation of the effect of aromatherapy with Rosa damascena Mill. on postoperative pain intensity in hospitalized children in selected hospitals affiliated to Isfahan University of Medical Sciences in 2013: A randomized clinical trial. Iranian journal of nursing and midwifery research. 2015;20(2):247.